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Editorial

Pitfalls in Interpreting Coronary Artery Statistics

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Statistical studies are of great value in medicine. They underlie many of our concepts in the diagnosis, prognosis, and treatment of disease. It is also well known that statistical studies may be misleading. This is particularly true of problems relative to coronary artery disease. Many conflicting reports appear concerning the immediate mortality from acute coronary thrombosis with myocardial infarction and the estimated life expectancy after recovery from myocardial infarction, and even the average length of life of patients with angina pectoris. There are obvious errors that explain some of the discrepancies which are often overlooked. One should at least focus one's attention on these simple aspects of the problem when reading about or investigating cases of coronary artery disease.

The average length of life after the onset of symptoms may be much longer in one series of cases of angina pectoris than in another, not because treatment has been any better or the disease any milder, but merely because the history has been taken more accurately. I have seen many patients who were thought to have had coronary symptoms beginning at a certain time, possibly with the onset of an acute myocardial infarction. However, when questioned very carefully, such patients would then recall coronary symptoms which had occurred two or three years before the date first mentioned. These early symptoms may be remembered only after the patient is asked a question such as the following: "When did you first *ever* feel any discomfort like this, even mild in degree, possibly on hurrying in cold air?" Only then may the patient reply: "Four years ago I had some mild chest distress one winter on hurrying uphill, and I had to stop." With a more careful taking of the history, one observer may calculate the length of life of such patients to be three or four years longer than the time estimated by another observer. This increased longevity might be ascribed erroneously to a special type of treatment.

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Another error stems from the type of physician who is reporting the results. Consultants often are those who have large series of cases to report. However, the consultant is more apt to be called to see the sicker patients. Therefore, his material would be weighted in favor of a poor prognosis and would not give a true average picture of the problem. The same is true of statistics obtained from large public or general hospitals. Here also the severer cases are found, since many of the milder ones are cared for by the home physician.

The readiness of the physician or consultant in seeing the patient has an important bearing on the statistics of coronary artery disease. For example, when a consultant who is either busy or selective in his practice is called on a Tuesday to see a patient with acute coronary thrombosis, he may reply that he cannot examine the patient before the coming weekend. He may thereby fail to have among his patients those who die in the first few days. The consultant who answers the call promptly will see the aforementioned hypothetical case on Tuesday evening. If the case proves to be fatal on Wednesday, it will be included in the statistics of the one physician and not in those of the other. One physician will have poorer statistical figures for immediate mortality of acute coronary thrombosis, not because his treatment is any worse, but because he is quicker in response to the call for his services.

Another difficulty in comparing one statistical study with another is the manner of determining the criteria for diagnosis. If one is dealing with cases of myocardial infarction, one physician, because he is an expert in electrocardiography, will include in his series instances that seem very definite to him, while another physician will regard these same instances as very questionable, merely because the latter physician has less confidence in his knowledge of electrocardiography. The former may rightly include in his group cases that never had a really severe acute illness, never had taken to bed, and yet actually had had a mild infarction. The other physician will be limiting his cases to those who show more convincing evidence of myocardial infarction. Thus, there will be more seriously ill patients in one group than in the other.

Another possible error that may arise in interpreting coronary statistics revolves about the average age of the population from which the coronary cases are drawn. The average age at onset and the age at death often are used as indices of the severity of the disease. Obviously, younger patients, or those who live only a short time with the disease, are more severely stricken. In this regard, it is necessary to know the average age of the noncoronary patients from among whom the cardiac patients have been selected. The average age at death from coronary disease in a home for the aged will be much greater than the average age for the general population. Contrariwise, the average age at death from coronary disease in the United States Armed Forces during the Second World War might well have been twenty-eight years. That does not mean that military life was in any way to blame for the coronary deaths at such a young age. It merely was the result of the fact that the average age of the entire military population was probably around twenty-eight years. The same figure probably would have been found for the age at death from measles.

Estimating the length of life after the onset of symptoms or after recovery

from the first attack of coronary thrombosis involves other, more subtle pitfalls that need to be avoided or carefully considered. Mention has already been made of the increased duration of coronary disease if a more careful history is taken and the onset of the disease can be antedated significantly. Another error made is that of including in such statistical analyses patients who already have lived two, five, and even ten or more years after onset of the disease before they are first seen by the physician who is making the study. When this happens the data is weighted toward more favorable figures, because the patient has already lived for some years and could not have been included among consecutive new cases if he had died in the first few months or years after the onset of the disease. This statistical error is particularly common and misleading in estimating the life expectancy after recovery from the first attack of acute myocardial infarction. In such a study, not only must the diagnosis be accurate and the fact be established that the episode is the first one, but the patient must be one of a consecutive series of patients, all of whom have been seen by the investigating physician during the first acute attack. In most such reviews the reporting physician includes patients who had their first attack under the care of some other physician, years before they were first seen by him. The diagnosis of their first attack was correct, but they had recovered and were now coming to another physician (generally a consultant) for the first time, five or more years later. When such cases are included in a series of consecutive patients who have recovered from their first attack of myocardial infarction, the data are distorted in a favorable direction. It is as though those patients were given a bonus of several years in the calculation, because if they had died during the first year after the recovery from the infarction, they never would have seen the consultant and could not have been included as long-lived patients. Consequently, most published surveys of life expectancy following a first myocardial infarction give figures that are two, three, or more years greater than the actual average. In other words, the only method of obtaining the true figures is to include only those consecutive patients who were actually seen during the acute attack by the physician making the study, and who recovered. This is best accomplished by a general practitioner who is likely to see the cases in his community, mild or severe, right from the onset of the illness. The only difficulty then is that in regard to a patient who drops dead suddenly without any previous history or without ever seeing a physician about his heart. Errors arising from this type of situation can be corrected only if all coroner's cases and all patients who die suddenly and on whom postmortem examinations have been made, are carefully studied and included in such a survey.

These are some of the difficulties and pitfalls in compiling and interpreting statistics concerning coronary artery disease. No doubt there are others not discussed here. They all help to explain some of the divergent findings and views that are published. In a word, it is a matter of proper and equitable sampling when different groups are compared. It is obvious that great caution must be exercised, particularly in drawing inferences from statistics as to the value of therapy, either medical or surgical, on the life expectance in cases of coronary artery disease.

Cardiac Output Measurement by the Injection Method Without Arterial Sampling

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1. INTRODUCTION

In the original injection method, as introduced by Stewart,[8] in 1921, an indicator is injected intravenously, and the arterial concentration of this indicator measured as a function of time by taking samples of blood every 2 seconds or so for about 1 minute. Cardiac output is then calculated by dividing the known amount of indicator by the integral of the primary part of the concentration-time curve, that is, that part of the curve belonging to the indicator passing the sampling site for the first time.

If a radioactive indicator, emitting γ-rays is used, the concentration-time curve can be measured outside the body by recording with a counter the radioactivity as a function of time, thus making arterial sampling superfluous. The theory predicts that the weighted mean of the concentration of indicator in any number of blood vessels can be measured as a function of time and used for calculating cardiac output in the same way as mentioned above (Burger[1] and van der Feer[2]).

To enable separation of the primary part of the counting rate-time curve obtained in this way, there must be present a sufficiently high peak belonging to the indicator that passes for the first time. For a curve to be good this peak must be short and high. Extrapolation will be easy then, and relatively unimportant, because the area of the extrapolated part will be small in comparison with the area of the measured part.

For a certain injection site and a short injection the quality of the curve depends on the choice of the part of the body that is taken as the measuring volume. Two properties of this volume are important: first, the time interval

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in which the indicator arrives at the different inflows of the measuring volume, and, second, the time it takes the indicator to traverse the measuring volume. Both have to be small in comparison with the mean circulation time of the whole circulatory system.

The "traversal time" is determined mainly by the size of the measuring volume. This volume can be made small by restricting the sensitive solid angle of the counter by a lead collimator. The spread of arrival times can be made small only by suitable choice of the measuring site, because the site will determine which blood vessels are chosen as measuring volume.

The experiments described here aimed to determine which regions of the human body give suitable curves, and to check the obtained values for cardiac output by the classical sampling method. Blood was therefore sampled from the brachial or femoral artery and the radioactivity measured continuously.

For the indirect measurements, calibration of the counter sensitivity in the position in which it is used is necessary. This was obtained by measuring the counting rate when the concentration of indicator had become uniform in the whole circulation. Since this uniform concentration is reached about 5 minutes after the injection, the indicator used is not allowed to leave the circulation in any appreciable amount during this period. We therefore made use of human serum albumin, iodinated with I^{131}, which leaves the blood plasma at a rate of 0.1 per cent per minute (Wasserman[10]).

Since the amount of indicator that can be given is limited by the radiation dose received by the patient, we made use of scintillation counters, which are much more sensitive than the simple Geiger counters. The largest dose is received by the blood of the patient. With the usual approximations (Mayneord[6]) this was calculated for an injection of 50 μc of I^{131} (the amount used by us) to about 1 roentgen, from which 0.5 roentgen is received in the first week after the injection.

The blood sampled was led past the crystal of one of the counters, with a constant flow rate obtained by a motor-driven syringe. Cardiac output was then calculated from the direct and from the indirect counting rate-time curve obtained simultaneously with one and the same injection of radioactive indicator.

2. EQUIPMENT

The scintillation counters used were of conventional design. A Tl-activated sodium iodide crystal of 35 mm. diameter and 25 mm. thickness was cemented on top of a photomultiplier (E.M.I. type 6260). Crystal and multiplier were mounted together in a lead cylinder having an outer diameter of 130 mm. and a wall thickness of 35 mm. The top of this cylinder was closed by an aluminum sheet (1 mm.); the free end of the crystal rested against this sheet. On top of the lead cylinder a lead collimator, 20 or 35 mm. thick, could be mounted, having an aperture of 35 mm. and giving a half-value angle for I^{131} radiation of 45° and 25°, respectively.

Pulses from the photomultiplier were equalized and recorded on photographic paper running at a speed of 3 cm. per second. From this record the counting rate-time curve, as well as the integral of this curve, could be easily deduced.

Continuous sampling was done through an arterial needle inserted into the brachial or femoral artery. This needle was connected to stainless steel tubing, 55 cm. long and of 2 mm. bore, by means of polyethylene tubing, 35 cm. long and of 2 mm. bore. The stainless steel tubing was wound two and a half turns around the sodium iodide crystal of one of the scintillation counters

and the free end connected to a motor-driven syringe by means of another piece of polyethylene tubing. Steel tubing and crystal were completely shielded by 35 mm. of lead. The all-metal syringe had a capacity of 50 cm.^{3}, and the plunger was driven with a velocity that resulted in a constant pumping speed of 0.8 cm.^{3} per second. Dimensions and flow rate were chosen so that the response time of the sampling device was about 2 seconds. This was measured by pumping water containing I^{131} through the device and introducing a sudden change in I^{131} concentration at the inflow of the arterial needle. For measuring the integral of the primary curve the value of the response time is not important at all. In order to enable extrapolation of the downsloping part of the first peak, however, the response time must not be too long.

The activity of whole blood samples was determined by filling up a small, flat-bottomed bottle to a mark on the neck of the bottle and inserting it into the aperture of the scintillation counter head. The same bottle (contents about 3 cm.^{3}) was then filled with a standard solution of I^{131} of a known dilution factor, and the results obtained were compared. The filling of the bottle is not at all critical, owing to its shape, and I^{131} concentrations could be measured with an accuracy better than 1 per cent. The blood samples were hemolyzed by cooling at $-10°C$. After rewarming, a homogeneous solution is obtained. This was done because red cells would otherwise accumulate at the bottom of the bottle, resulting in a too low counting rate as compared with a homogeneous distribution of red cells, and thus of the active plasma.

Normally, the measurements on patients were made with three scintillation counters. One was used for measuring the activity of the sampled blood, and the other two for indirect measurement of concentration-time curves.

3. PROCEDURE

The solution of iodinated human serum albumin was diluted with saline to a concentration of about 50 μc per cm.^{3}. Two syringes were filled with 1 cm.^{3} of this solution and weighed. One was used for the venous injection, and the other was diluted with 5 L. of water for calibrating purposes. After they had been used, the empty syringes were reweighed, in order to know the exact amount injected into the patient and the calibrating solution.

The sampling device was flushed with a sterile isotonic solution of citrate of sodium (3.6 per cent), which appeared to prevent clotting during the measurement. The counters were then brought into position and the arterial needle was inserted. After inserting the injection needle into a cubital vein, the stylette of the arterial needle was removed and the sampling device connected. Next, the recording camera was switched on, the indicator injected in about 1 second, and the motor of the sampling device switched on.

At the end of the sampling period (about 1 minute) the sampling device was disconnected from the arterial needle and flushed again with the solution of citrate of sodium.

About 4 minutes after the injection, the recording camera was switched off, and a 5-cm.^{3} sample of blood was taken through the arterial needle. The concentration of I^{131} in this sample was measured as described in Section 2. The sampling device was then filled with the standard dilution and its counting rate determined.

To avoid uptake of free I^{131} by the thyroid gland, the patient was given 1 Gm. of potassium iodide before the measurement, and 0.5 Gm. daily for 3 weeks thereafter.

4. CALCULATION OF CARDIAC OUTPUT

Cardiac output is then calculated from the above-described measurements with the formula:

$$F = \frac{M\ U_o}{c_o \int_{t=0}^{\infty} U(t)dt} \qquad (1)$$

in which M is the amount of indicator injected, U_o the counting rate obtained when the measuring

volume is filled with the concentration c_o, and $\int_{t=0}^{\infty} U(t)dt$ the integral of the primary counting rate-time curve (Burger[1]).

If M_p denotes the amount of indicator injected into the patient, M_s the amount of indicator used for the standard solution, U_s the counting rate measured when the sampling device is filled with the standard dilution, the output in cubed centimeters per second calculated from the sampling curve is given by:

$$F_{art} = \frac{M_p\ U_p}{\frac{M_s}{5{,}000} \cdot \frac{N_p}{N_s} \int_{t=0}^{\infty} U(t)dt} = \frac{5{,}000\ U_s}{\int_{t=0}^{\infty} U(t)dt} \cdot \frac{M_p}{M_s} \tag{2}$$

In this formula, U_s is measured in counts per second, and the integral of the arterial counting rate-time curve in number of counts.

The output calculated from an indirectly measured concentration-time curve is given by:

$$F_{ind} = \frac{M_p\ U_p}{\frac{M_s}{5{,}000} \cdot \frac{N_p}{N_s} \int_{t=0}^{\infty} U(t)dt} = \frac{5{,}000\ U_p}{\int_{t=0}^{\infty} U(t)dt} \cdot \frac{M_p}{M_s} \cdot \frac{N_s}{N_p} \tag{3}$$

where U_p is the counting rate measured when a homogeneous concentration is reached in the patient, N_s and N_p are the counting rates measured for the small sampling bottle filled with standard solution and patient's blood, respectively.

The blood of the patient is given by:

$$V_p = \frac{M_p}{M_s} \cdot \frac{N_s}{N_p} \cdot 5{,}000 \tag{4}$$

If this is substituted in (3), the following simple expression is obtained for F_{ind}:

$$F_{ind} = \frac{V_p U_p}{\int_{t=0}^{\infty} U(t)dt} \tag{5}$$

If the value obtained for F_{ind} is to be checked by the value F_{art} obtained by the classical sampling method, F_{ind}/F_{art} is of interest only. If the two counting rate-time curves U(t) are measured simultaneously with one injection of radioactive material, it can be seen from formulae (2) and (3) that it is not necessary to know the amounts M_p and M_s injected into patient and standard, respectively.

If one indirect value is to be checked by another indirect value measured simultaneously, even the finally reached concentration in patient's blood (values of N_s and N_p) need not be known.

5. COMPARATIVE MEASUREMENTS ON PATIENTS

It has been poiuted out that it is the choice of a measuring site that mainly determines whether a successful counting rate-time curve will be found. With the scintillation counter described in Section 2, using a collimator 35 mm. in thickness, such a curve was obtained only if the counter head was directed toward the heart or toward the head of the patient. For all other parts of the trunk, as well as parts of an arm or leg, the measured curve showed a steady rise to a final value without showing a peak. Therefore, only head and heart curves were measured simultaneously with an arterial sampling curve.

All patients were in the supine position during the measurements. The head curves were made with the counter axis in the horizontal position and the aperture of the collimator pressed against the ear. The 35-mm. collimator was used in order to restrict the measuring volume to the head alone. It is necessary to choose the right ear if the injection is made into the right arm, otherwise the counter can "see" the right shoulder and, therefore, the indicator going from the right arm to the right heart will contribute to the concentration-time curve. This is not allowed to happen, since the indicator must first pass the main branch before its concentration is measured.

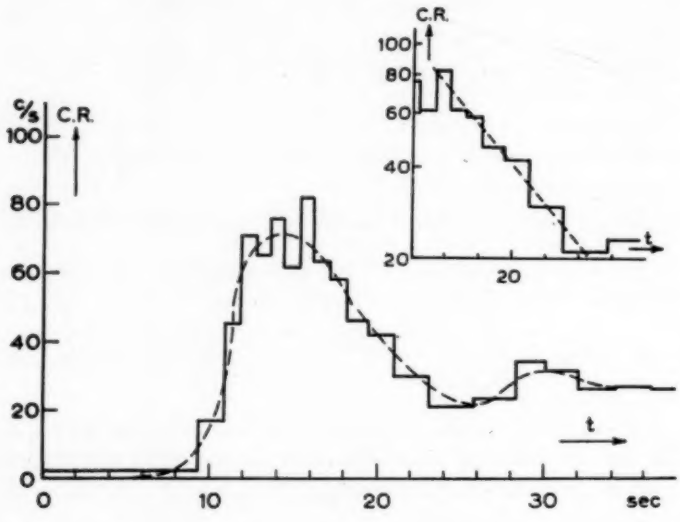

Fig. 1.—Typical counting rate-time curve obtained from the head counter. The downsloping part is plotted separately on a semilogarithmic scale.

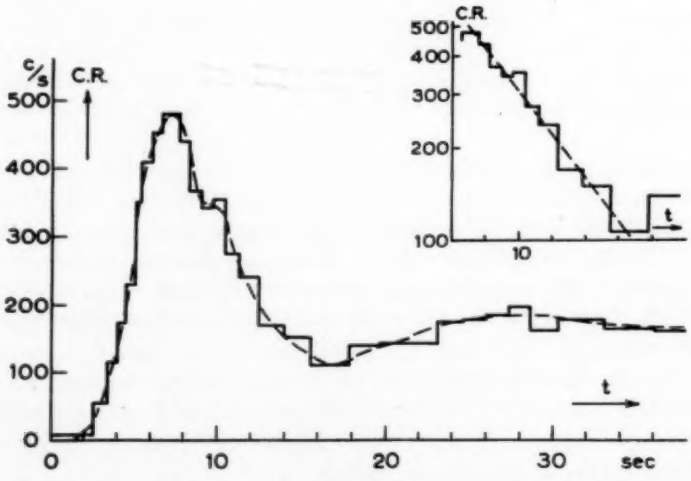

Fig. 2.—Typical heart curve measured on the same person as in Fig. 1, with the same injection.

The heart curves were measured with the counter axis in the vertical position and the aperture of the 20-mm. collimator above the center of the frontal heart projection, which was determined by percussion. The counter head was just free from the skin, in order to give the patient room for breathing. The 20-mm. collimator was used because the counting rates obtained with it were considerably higher than those with the 35-mm. one.

Typical head, heart, and arterial sampling curves measured simultaneously in one patient with one injection of radioactive material are given in Figs. 1, 2, and 3, respectively.

If cardiac output is to be calculated from these curves, it is necessary to adopt some type of extrapolation of the downslope of the first peak. For arterial sampling curves the exponential extrapolation is a successful method for most cases. Since the downslope of the majority of our head and heart curves clearly showed an exponential part, we used the exponential extrapolation for all our curves.

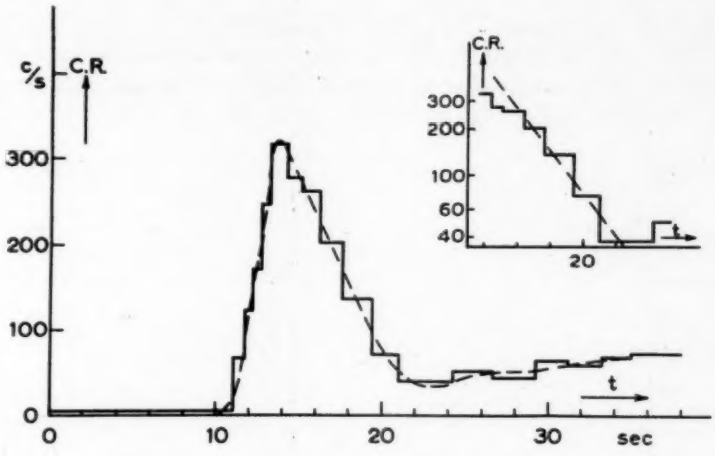

Fig. 3.—Typical arterial sampling curve measured on the same person as in Figs. 1 and 2, with the same injection.

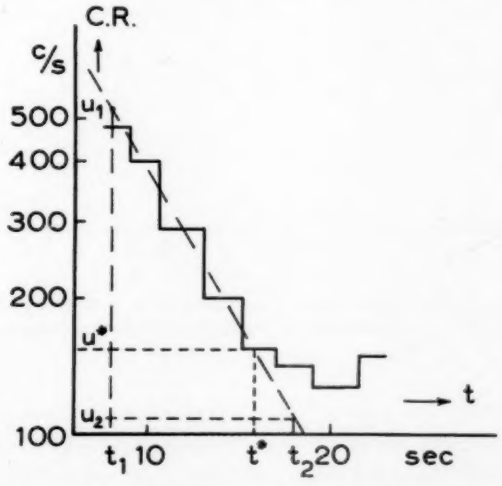

Fig. 4.—Plot of the downsloping part of a counting rate-time curve on a semilogarithmic scale.

The integral of the primary counting rate-time curve was determined by plotting the downsloping part on semilogarithmic paper. The integral of the measured part of this curve is obtained simply by counting on the record the number of pulses from time zero to t*, where the measured curve leaves the straight line (Fig. 4). The number of counts obtained in this way must be diminished by the number of background counts over this same period.

If the exponential part is written as:

$$U = U\, e^{-\lambda(t - t^*)}$$

the integral of the extrapolated part is given by U^*/λ where U^* is the deflection at time t^* and λ is given by:

$$\lambda = \frac{1}{t_2 - t_1} 1n \frac{U_1}{U_2}$$

where 1 and 2 are two arbitrary points on the straight line that is drawn through the measuring points (Fig. 4).

The results of the measurements in patients are presented in two scatter diagrams. In Fig. 5 the cardiac output values calculated from the head curves are compared with the values calculated from the arterial sampling curves. In Fig. 6, heart values are compared with arterial values.

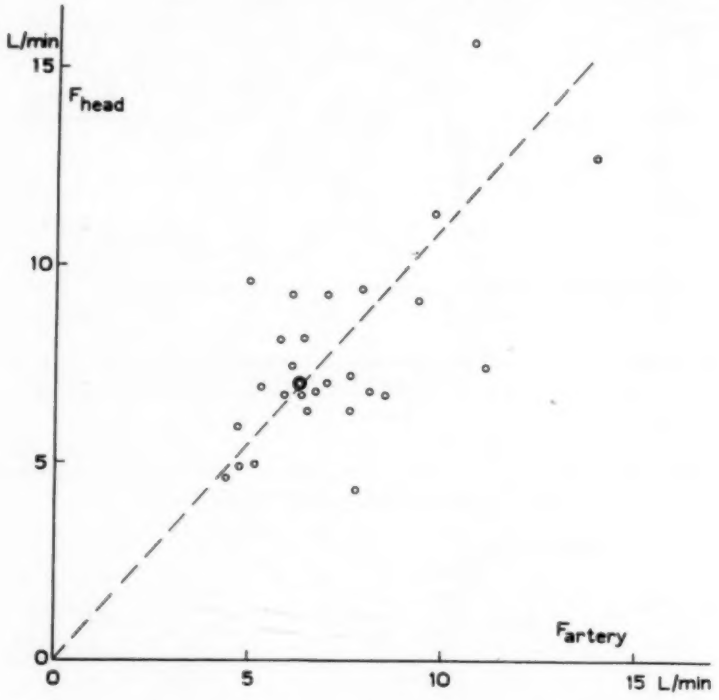

Fig. 5.—Comparison of cardiac output values calculated from a head curve and an arterial sampling curve in 29 cases. The two concentric circles represent two cases with identical values.

6. DISCUSSION

To get an idea of the validity of the cardiac output values calculated from an indirectly measured head or heart curve, it is assumed that the relation between arterial and head values (Fig. 5) and between arterial and heart values (Fig. 6) is given by a straight line going through the origin. So we make the fairly reasonable assumptions that the random errors of arterial, head, and heart values measured simultaneously are independent of one another, and that the random as well as the systematic errors are proportional to the value of cardiac output.

The mean value of 100 $(F_{head} - F_{art})/F_{art}$ for all 29 measurements of Fig. 5 was calculated to +10 per cent, with a standard deviation of 5 per cent. The relation between F_{head} and F_{art} is, therefore, $F_{head} = 1.10\ F_{art}$ (dashed line in

Fig. 5). The standard deviation of one comparison is 27 per cent. Since the standard deviation of F_{art} is not more than 15 per cent (van der Feer[2]), the standard deviation of F_{head} is more than 23 per cent ($23^2 = 27^2 - 15^2$).

The mean value of 100 $(F_{heart} - F_{art})/F_{art}$ for all 33 measurements of Fig. 6 was calculated to +13 per cent, with a standard deviation 2.5 per cent. Thus, $F_{heart} = 1.13\ F_{art}$. The standard deviation of one comparison is 15 per cent. This means that the standard deviation of F_{heart} is of about the same size as the standard deviation of F_{art}, or it may be even smaller. Therefore, we also calculated the mean value of 100 $(F_{art} - F_{heart})/F_{heart}$. This gives the relation $F_{heart} = 1.11\ F_{art}$ and a standard deviation of one comparison of 12 per cent.

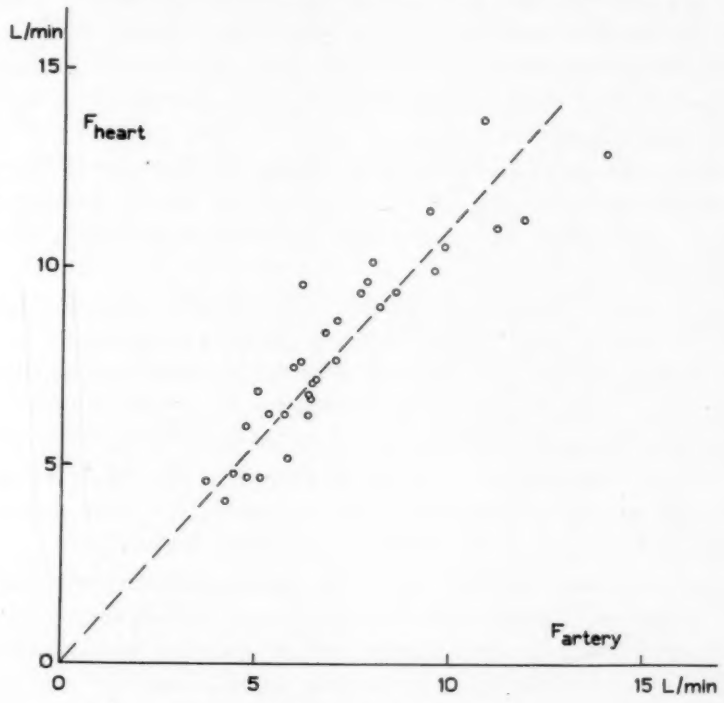

Fig. 6.—Comparison of cardiac output values calculated from a heart curve and an arterial sampling curve in 33 cases.

The dashed line in Fig. 6 represents the mean of the two relations, that is, $F_{heart} = 1.12\ F_{art}$. The standard deviation of F_{heart} cannot be evaluated without knowing more about the standard deviation of F_{art} in this particular case. If we assume, however, that both standard deviations are of about the same size, 10 per cent ($10^2 + 10^2 = 15^2$) is a good approximation,

So our final conclusion is that an indirectly measured head curve could be used for calculating cardiac output, but it is not very successful because of the rather high standard deviation of the result, that is, about 25 per cent.

An indirectly measured heart curve, however, can replace successfully an arterial sampling curve. Because of the systematic error of +12 per cent, the cardiac output value calculated from a heart curve must be corrected with −11 per cent. The standard deviation of the result is about 10 per cent.

These figures may be compared with the material presented by others. Huff[3] checked output values calculated from an indirectly measured heart curve against the direct Fick method, in dogs. Albumin iodinated with I^{131} was used, and the scintillation counter was well collimated with a 5-cm. collimator having an aperture of 2 cm. in diameter. The curves were extrapolated exponentially. In 22 measurements no systematic error between the two methods was found. From his material we calculated a standard deviation of 21 per cent for one comparison.

Pritchard[7] compared indirectly measured heart curves with arterial sampling curves in about the same way as we did. With a well-collimated scintillation counter, exponential extrapolation of the heart curves was possible, and a good agreement between the two output values was found. For 33 out of 39 measurements the difference was not more than 7 per cent. Unfortunately no more figures were given in this short abstract, and, therefore, no standard deviation could be calculated.

The same comparisons were made by Mack[5] in 10 cases. The curves were also extrapolated exponentially. No systematic difference between heart and arterial values was found. We calculated a standard deviation of 13 per cent for one comparison.

Shackman[4a] made 61 comparisons of cardiac output values calculated from an indirectly measured heart curve with the direct Fick method, in man. The scintillation counter used had a collimator of 5-cm. thickness, with an aperture of 2.5-cm. diameter, which gives a half-value angle of 23° (Veall[9]). The mean difference between the two methods is reported as 175 $cm.^3$ per minute, with an error of 134 $cm.^3$ per minute. If we assume that the mean value of cardiac output is 6 L. per minute, this means that the systematic error is 3 ± 2 per cent and the standard deviation of one comparison about 15 per cent.

The figures mentioned above are all in good agreement with our own findings, except for the systematic error of 12 per cent. This error is due probably to the solid angle of our heart counter, which is rather wide (half-value angle of 45°). Thereby the calibrating deflection of this counter may be too high because the counter is capable of observing too many blood vessels which do not contribute to the first peak of the concentration-time curve. Therefore, the use of a collimator that gives a half-value angle of not more than 25° is recommended. This necessitates, however, directing the counter toward the heart accurately.

The presence of a systematic error in our heart and head values actually means that the type of extrapolation used is not the right one. That the exponential extrapolation can be used for a heart curve measured with a highly collimated counter can be understood as follows. The heart counter, sufficiently collimated, chiefly measures the concentration of indicator in the heart. The downslope of the primary part is mainly determined by the concentration of the left heart. Since the shape of the concentration-time curve of the left heart is not very different from the shape of the concentration-time curve in the big arteries, it is not surprising that the exponential extrapolation is so successful. The downslope of a head curve, however, consists of contributions from the

whole head and is exponential probably only in the first approximation. Thus, a systematic error is introduced by using the exponential extrapolation.

The great difference in standard deviation of heart and head values probably may be attributed also to the extrapolation, since the slope of the straight line drawn on semilogarithmic paper is less accurate in the case of a head curve because of the lower counting rate.

SUMMARY

Cardiac output was measured by the injection method, using I^{131}-labeled human serum albumin as indicator, and measuring concentration-time curves through the intact skin with a collimated scintillation counter. Although, in principle, any number of blood vessels could be used as the measuring site, it was found that because of recirculation, suitable curves were obtained only if the counter was directed toward the head or the heart. Cardiac output values calculated from these curves were compared with values found with the classical sampling method. Head, heart, and arterial sampling curves were measured simultaneously with one injection of radioactive indicator.

The measurements show that a head curve could be used in measuring cardiac output by the injection method, but it is not very successful because of the rather high standard deviation of the result (25 per cent). A heart curve, however, can successfully replace an arterial sampling curve. The accuracy of heart and arterial values is about the same (standard deviation 10 per cent). The systematic error of +12 per cent found for our heart values might be reduced by using a collimator that gives the counter a half-value angle of not more than 25°.

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Serum Electrolyte Observations Following Extracorporeal Circulation

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Surgery of the open heart using an extracorporeal circulation is a relatively recent technique, and like all new procedures, it has brought with it many questions to be answered and problems to be solved. One of the problems to be solved is that of postoperative acidosis. Cohen,[1] Clowes,[2] Kolff,[3] Ito,[4] and Callaghan,[5] using a variety of pump-oxygenators, have all described a metabolic acidosis which occurred sometime after a perfusion. The purpose of this paper is to present our experiences in regard to electrolyte changes after perfusion and to present our ideas concerning such changes.

THE STUDY

Data were obtained from 65 consecutive patients operated during the period from July, 1957 to April, 1958. The Osborn-Gerbode modification of the blood-film pump-oxygenator and the Melrose rotating-drum blood-film pump-oxygenator were used to provide the extracorporeal circulation and oxygenation. The duration of perfusion was, generally, about 30 minutes, the shortest being 5 minutes and the longest 108 minutes. The blood for analysis was drawn in a heparinized syringe from an indwelling catheter placed in the inferior vena cava.

Nine patients were used for a detailed study. Control blood samples were obtained from the peripheral veins of these patients on the day before surgery.

The first postoperative sample of blood was usually taken upon the patient's arrival in the recovery room, about 1½ to 2 hours after the end of perfusion. A second postoperative sample was taken 4 to 6 hours later. It was felt that any samples taken while the patient was still on the operating table would reflect the anesthetist's vigor in aerating the patient's lungs rather than the patient's regulatory mechanisms. Additional data were obtained from the remaining patients. Blood samples were taken from most of these patients on one or two occasions during the first 10 hours after arrival in the recovery room.

Blood was drawn into the heparinized syringe without introduction of air and was immediately analyzed for pH, using the Cambridge Model R pH meter. The pH values are those read directly from the machine without correction for temperature. Because of this, the control values are in the range of 7.45 to 7.62. The packed red cell volume was also determined on this blood by the capillary tube micromethod, using the Drummond microhematocrit centrifuge and reader.

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The remainder of the blood was centrifuged, the plasma being used to determine the carbon-dioxide, chloride, and total base values by the Scribner bedside method.[6-8] Sodium was calculated by subtracting 12 mEq./L. from the total base value. Potassium was determined in the routine hospital chemistry laboratory, using a Baird-type flame photometer.

Determinations of blood lactic acid were made on blood from 17 patients. Control values were obtained from blood drawn from the anesthetized patients at the start of surgery, before perfusion; then, samples were drawn immediately after perfusion, and also several hours later in some cases. In addition, determinations of lactic acid were made on 4 occasions on pooled donor blood before perfusion. The method used for determination was that of Barker and Summerson.[9] By this method, normal values are 20 mg. per cent for the resting individual and 100 mg. per cent or more after severe exercise.

RESULTS

pH Changes.—In 8 patients studied in detail, pH values were found to rise in 2, fall in 4, and not change in 1 (Fig. 1). Plotting the means of these values, we see a mean reduction in pH of 0.08, 2 hours postperfusion. At 6 hours postperfusion all but 1 of the 8 patients had an increase in pH, and the mean pH value has risen slightly toward normal. Additional data from 22 patients confirm these figures.

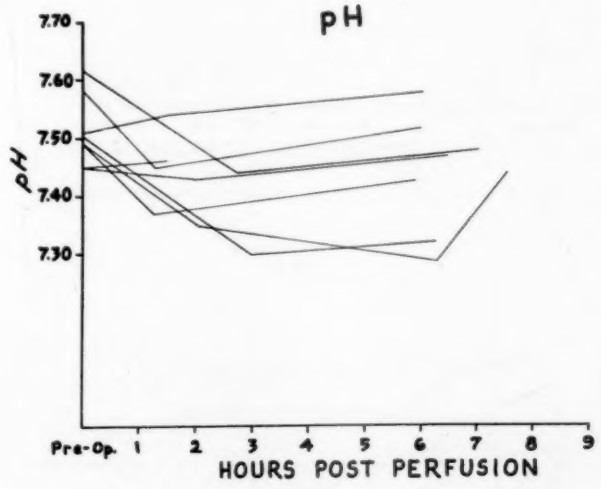

Fig. 1.—Changes in pH after perfusion.

Carbon-Dioxide Changes.—Seven of 9 patients studied showed a fall in serum CO_2 content, 2 hours postperfusion, as compared to their preoperative values (Fig. 2). When the mean values were plotted, the preoperative mean CO_2 content was 26 mEq./L. The value at 2 hours postperfusion was 23.5 mEq./L. Four hours later the mean CO_2 content had risen to 24 mEq./L. In the same 4-hour period, 4 patients showed a further drop in CO_2 content, 3 showed a rise, and 2 showed no change when compared to the 2-hour values. If the data obtained from 42 additional patients were added to the graph showing the figures summarized above, it would not change the mean value curve.

Chloride, Sodium, and Potassium Changes.—Chloride, sodium, and potassium all showed a slight drop in the immediate postoperative period. In all 9 patients the chloride concentration was lower 2 hours postperfusion than preoperatively.

At 6 hours postperfusion the chloride concentration in the blood of 6 patients was somewhat lower than at 2 hours. In 1 patient it had risen. When all 51 cases in which chloride was measured were compiled (Fig. 3), it appeared that a mean preoperative chloride concentration of 107 mEq./L. had occurred. Two and one-half hours postperfusion the mean concentration was 105 mEq./L., and 6½ hours postperfusion it was 102 mEq./L.

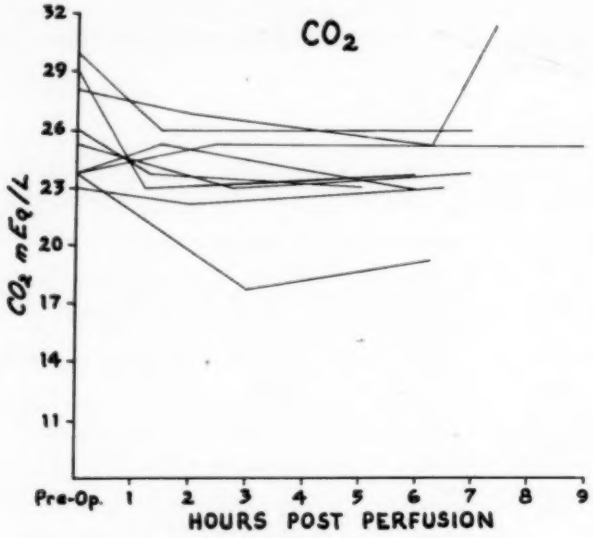

Fig. 2.—Changes in carbon dioxide after perfusion.

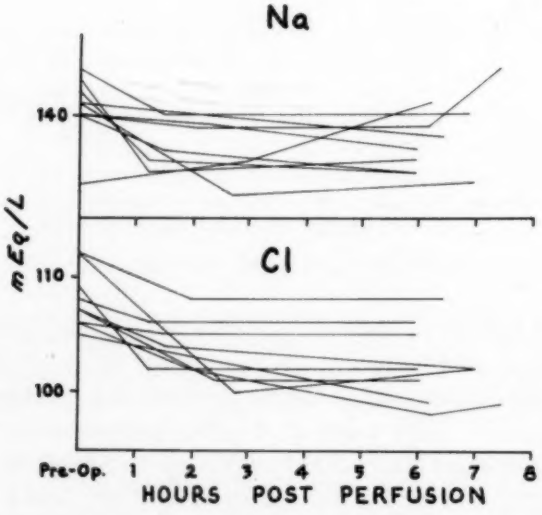

Fig. 3.—Changes in sodium and chloride after perfusion.

The serum sodium concentration studied in the same manner gave the results shown in Fig. 3. Although there is a decided downward trend in sodium concentration from preperfusion values to the 2-hour postperfusion values, 1 of the 9 patients studied showed a rise in serum sodium.

The mean values for all 51 patients studied showed, during this period, a fall from a preoperative value of 140 mEq./L. to 137 mEq./L., 2 hours post-perfusion. During the next 4 hours the mean values decreased by another 0.5 mEq./L., and 4 of the 9 patients also showed a slight decrease in serum sodium; 3 others showed a slight rise in concentration of sodium.

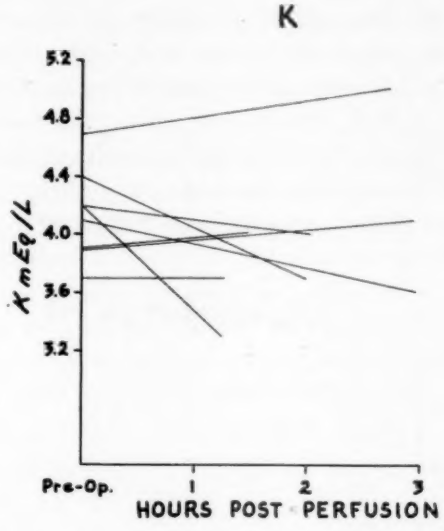

Fig. 4.—Changes in potassium after perfusion.

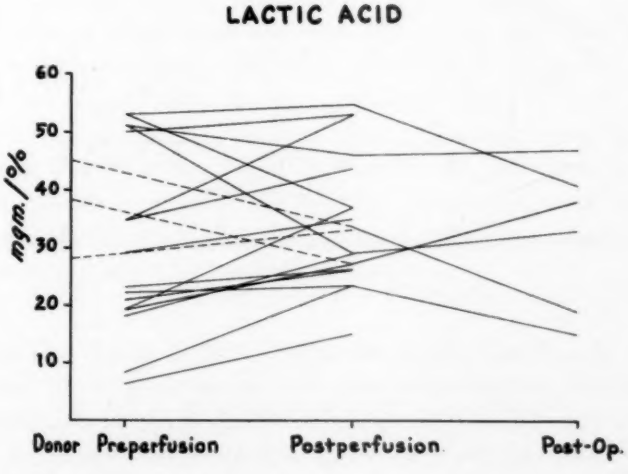

Fig. 5.—Changes in lactic acid after perfusion. The broken line represents the change in lactic acid content between the pooled donor blood before perfusion and the postperfusion value in the patient.

The potassium study involved 23 patients, 8 of whom had pre- and post-perfusion determinations (Fig. 4). Four of these had a fall in serum potassium, 3 had a rise, and 1 had no change. When the mean values for all the patients were calculated, it showed that there was a preperfusion concentration of serum potassium of 4.15 mEq./L., and that 2½ hours later it was 3.95 mEq./L.

Lactic Acid.—In 12 patients from whom blood samples were taken before perfusion, but while they were under anesthesia, and again immediately after perfusion, 11 showed a rise in blood lactic acid levels and 3 showed a fall (Fig. 5). In 2 of the 3 which showed a fall in lactic acid, more than one preperfusion sample had been taken: one which was higher and one which was lower than postperfusion values. Six patients also had lactic acid determined from 2 to 5 hours after perfusion. Of these, 3 patients showed an increase in lactic acid and 3 showed a decrease. The mean values for these determinations showed a preperfusion level of 26 mg. per cent and a postperfusion level of 36 mg. per cent, and at 3¼ hours postperfusion, 32 mg. per cent. On 4 occasions, samples were drawn from the pooled donor blood in the heart-lung machine just before perfusion. The mean lactic acid level of this blood was 33 mg. per cent. In 3 of these 4 cases, blood was drawn after perfusion, and 2 showed a decrease in lactic acid, while 1 showed an increase.

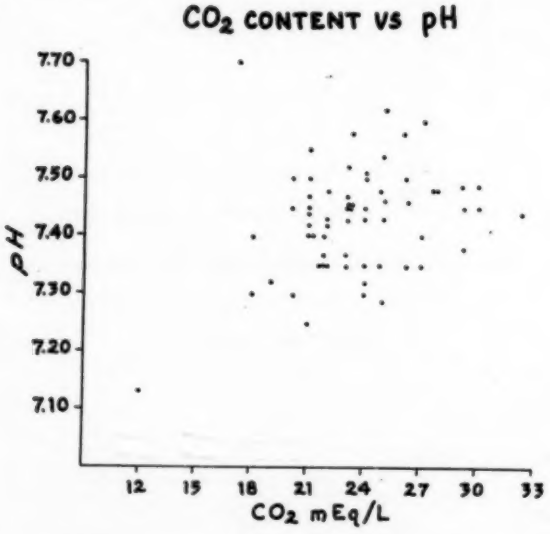

Fig. 6.—Observed carbon-dioxide content plotted against observed pH values.

DISCUSSION

The degree of acidosis which we have found is much less severe than that reported by Ito,[4] who showed a drop of a mean of 0.17 pH units in his nonhypotensive patients. In only 3 cases in our study have we considered the acidosis of such a degree as to require sodium lactate or sodium bicarbonate.

The determination of CO_2 content alone is of little value following perfusion with the pump-oxygenator, since the patients may suffer from either a metabolic or respiratory acidosis, or a combination of the two. The metabolic acidosis may occur as a result of ketosis from preoperative starvation or an accumulation of acid metabolites, such as lactic acid, during surgery. It is well known that the body tends to blow off CO_2 as a defense against metabolic acidosis.

Patients with thoracotomies are liable to develop a respiratory acidosis in the postoperative period. This could be due to a poor respiratory exchange.

Several factors which may contribute to this are: sedation, position in bed, decreased lung volume due to fluid collections in the chest, and voluntary splinting of the chest. These all tend to cause a retention of CO_2 and a respiratory acidosis.

It would appear now that the CO_2 content of the blood may be either high, low, or normal in the presence of an acidosis, depending on its cause.

Fig. 6 shows the poor correlation between blood pH and CO_2 content in all patients in which the two were obtained simultaneously.

Serum chloride, sodium, and potassium all show a slight drop in serum concentration in the immediate postoperative period. This is quite likely as a result of dilution of blood electrolytes by intravenous fluids and by water retention. Moore[10] has recently described this phenomenon well. The decrease in the mean serum potassium suggests that potassium is not released in any large quantity by hemolysis of red cells or tissue damage.

We offer one explanation for the increase in lactic acid content during perfusion. After extracorporeal circulation, radiochromium studies have shown that as much as 88 per cent of the patient's blood volume has come from donor blood and that, in effect, an exchange transfusion has taken place.[5] When we consider that the lactic acid content of the donor blood may be 30 to 40 per cent higher than that of the patient's own blood, it is not surprising that there is a rise in lactate during perfusion. However, there may be other reasons for a rise in the blood lactic acid.

SUMMARY

Our experience has shown that only minor changes occur in the serum electrolytes after open-heart surgery using an extracorporeal circulation. Although there is a slight acidosis and lowering of the CO_2 content, it is only rarely necessary to correct these. Because of poor correlation of CO_2 content and blood pH, measurement of the former is not helpful in diagnosing an acidosis after surgery. There is some postperfusion increase in the blood lactic acid, but much of this increase can be accounted for by the accumulation of lactic acid in the blood used to run the pump-oxygenator. No significant changes are seen in the potassium, chloride, or sodium content of serum.

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Effect of Acute Coronary Occlusion Upon the Movement of Evans Blue Dye Into Different Areas of Pig Heart Muscle

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Because it is rapidly and tenaciously bound to plasma protein, Evans blue dye has found widespread use in the estimation of total body plasma volume by dilution methods. Caster, Simon and Armstrong[1-3] have developed methods for the determination of the Evans blue space in tissue samples, and this has allowed the ready estimation of plasma volumes in each of the tissues of the body.[4] Although there is a slow movement of Evans blue to extravascular positions, kinetic studies suggest that, in large part, this problem can be avoided by injecting the dye no more than 4 to 5 minutes prior to stopping the circulation and removing the tissue samples for analysis. Under these conditions the Evans blue space in a variety of normal rat tissues was found to be quite constant. Hemodynamic alterations caused by gross alteration of the circulating plasma volume or by the injection of large doses of epinephrine resulted in marked changes in the Evans blue space in tissue.[4] The present data relate to an attempt to use this method to study the hemodynamic changes occurring in different portions of the pig heart following coronary occlusion.

PROCEDURE

Male pigs of unspecified breed, ranging in weight from 15 to 27 kilograms, were obtained from the South St. Paul stockyards shortly before each experiment. Under intraperitoneal chloral hydrate anesthesia (300 mg./Kg.) and standard surgical conditions, the left chest was opened. Ventilation was maintained through a transglottic airway. Immediately after tying the LAD (left anterior descending branch of the coronary artery) at the bifurcation, 65 ml. of 2 per cent Evans blue dye solution (made isotonic by adding sodium chloride) was injected into the azygous vein of the pig. The dye injection required approximately 1 minute. Blood samples for analysis were removed from the right ventricle of the heart at 5 minutes after the end of the dye injection or when the heart began to fibrillate (whichever time was shorter). In control animals the LAD was not tied. Immediately after the 5-minute blood sample was obtained, the heart was quickly

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excised and the blood in the chambers allowed to drain. Tissue samples were rapidly cut from the walls of the heart, blotted, and placed in weighing bottles. Samples for analysis[3] were taken from the following areas of the heart: two areas along the left anterior descending branch of the coronary in the wall of the left ventricle, one area just below the ligation (LAD high) and the other area about halfway between there and the apex (LAD low); two samples were taken from areas served by the left circumflex (LC high and LC low); one sample was taken from the area of the posterior descending branch (Post. Desc.); two areas were taken from the interventricular septum (Sept. high and Sept. low); the entire right atrium and entire left atrium were taken as single samples (Rt. Atr. and Lt. Atr.); and one or two samples were removed from the right ventricle in the area near the LAD (Rt. Vent. high and Rt. Vent. low). In each case the sample represented a cylindrical section cut straight through the muscular wall. About 1 to 2 mm. of the inner and outer surfaces were removed. The reason for this is related to the observation that the epicardium and endocardium have an Evans blue space that exceeds that of heart muscle by perhaps threefold to fourfold.

Quinidine exerts an antifibrillatory effect in the pig.[5] In an attempt to determine whether or not the protective ! enefit of quinidine was related to alterations of coronary blood flow, as reflected by changes in Evans blue space, some of the pigs were given intravenous quinidine (10 mg./ Kg.) 10 minutes prior to coronary occlusion.

Control Data.—Four control pigs (with open chest but no ligation) taken at intervals throughout the study serve to furnish a base line for the interpretation of the results of tissue analysis. Two received quinidine and two did not. Table I shows that the Evans blue space at different points in the ventricles averaged 3.5 ± 0.5 per cent of the fresh weight of the heart muscle.

TABLE I. PER CENT OF EVANS BLUE SPACE IN HEARTS OF CONTROL PIGS WITH AND WITHOUT QUINIDINE

TREATMENT	NUMBER OF SAMPLES	MEAN	S.D.
No quinidine	7	3.50	.56
	11	3.59	.52
Quinidine	5	3.58	.38
	6	3.38	.37

Table II summarizes the control data obtained for each analyzed area of the heart. In all but two ventricular areas the Evans blue space was 3.5 per cent of the fresh weight of the tissue, within the experimental error of the method. The large standard deviation associated with the atrial data probably reflects the difficulty in removing the outer 1 to 2 mm. of the surface of these samples in order to get a uniform sample for analysis.

TABLE II. PER CENT OF EVANS BLUE SPACE IN DIFFERENT PARTS OF THE HEART OF CONTROL PIGS

TISSUE	NUMBER OF PIGS	MEAN	S.D.
LAD high	2	4.12	.33
LAD low	1	3.84	—
Post. Desc.	2	3.24	.80
LC	4	3.52	.43
Sept. high	3	3.03	.32
Sept. low	3	3.67	.53
Rt. vent.	4	3.47	.28
Atria	4	3.70	1.53

The effect of coronary ligation upon Evans blue space is shown in Table III. There were statistically significant ($P < .01$) decreases in the Evans blue space in the areas grossly served by the occluded artery (LAD).

TABLE III. CHANGE IN EVANS BLUE SPACE OF PORTIONS OF THE HEART OBSERVED AFTER LIGATION OF THE LAD (LEFT ANTERIOR DESCENDING BRANCH OF THE CORONARY ARTERY)†

TISSUE	NUMBER OF SAMPLES	NUMBER OF PIGS	MEAN	DECREASE (PER CENT)	INCREASE (PER CENT)
LAD high	9	7	2.60**	26	
LAD low	9	7	1.36**	61	
Sept. high	6	6	1.19**	66	
Sept. low	8	7	2.23**	37	
Rt. Vent. high	6	6	2.44**	31	
Rt. Vent. low	6	6	2.64*	25	
LC high	5	3	4.30*		22
LC low	3	3	4.70*		34
Post. Desc.	5	5	4.47**		27
Rt. Atr.	6	6	5.54		55
Lt. Atr.	7	7	4.83		36

*$.05 \geq P > .01$

**$P < .01$

†Statistical comparisons in each case (see text) are with a control mean value of: Mean = 3.52, S.D. = .46, and N = 29.

In all but two cases (LAD high and Sept. high) it is appropriate to compare the experimental means directly with the normal control mean of 3.52 per cent Evans blue space (S.D. = 0.46 and N = 29). The decrease observed in the LAD high samples is significant when tested against either the pooled 3.52 per cent mean or the 4.12 per cent mean which was the observed control value for the LAD high. The Sept. high value likewise shows significant decreases when tested either against the pooled mean or against the control mean for the Sept. high sample.

In other areas, such as those served by the left circumflex and posterior descending branches, there were significant increases in Evans blue space. There were also increases in the Evans blue space of the right and left atria, but the standard deviations in these cases were sufficiently large so that statistical significance was not obtained.

In no case was there a significant difference between the Evans blue spaces observed in animals receiving quinidine and in those receiving none. In the ischemic areas the average decrease in Evans blue space was 55 and 47 per cent, respectively, for the quinidine and no-quinidine groups. In the nonischemic areas the corresponding average increases were 27 and 30 per cent. From this we conclude that the antifibrillatory action of quinidine does not operate by altering factors related to Evans blue space.

SUMMARY AND CONCLUSIONS

Ligation of the left anterior descending branch of the coronary artery results in a significant decrease in the Evans blue space in those parts of the myocardium served by this artery. Other areas showed a small but significant increase. The data indicate that the observed Evans blue space in all areas remained substantially constant from 2 to 6 minutes following LAD ligation. These observations are consistent with the suggestion that there is a continued and well-distributed blood flow through a substantial portion of the ischemic areas. The data tell nothing about the direction or source of this flow but do

show that it is rapid enough to provide equilibrium levels of Evans blue within the first minute or two after the completion of the dye injection.

The fact that quinidine did not affect the Evans blue space of ischemic or nonischemic areas suggests that its protective action is related to factors other than increases in blood supply.

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The Fine Structure of the Small Blood Vessels of Normal Human Dermis and Subcutis

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Although the physiology of blood vessels, especially capillaries, has received a great deal of attention, little work has been done until recently on the fine structure of endothelial cells. In 1953, Palade[8] made an electron microscopic study of the capillaries of the heart, intestine, pancreas, and skeletal muscle. He described in the endothelial cytoplasm two characteristic elements in addition to the usual structural components: fibrils of approximately 240 Å in diameter, and small vesicles about 650 Å in diameter. Palade suggested that the vesicles may represent a system for transporting fluids across the capillary walls.

Other workers, among whom are Policard,[11,12] Oberling,[6] DeGroodt,[1] Yamada,[13] and Pease,[9,10] have made careful studies of the specialized vessels of the kidney (glomerular and peritubular vessels). The endothelial cells of these vessels were found to be modified for their special functions by the presence of pores extending through the cells from the basement membrane to the vessel lumen. The endothelium of the pulmonary alveolar capillaries was found by Karrer[2] and Low[4] to be extremely attenuated except in the regions of the nuclei. This condition also appears to be specialization for their particular function.

More recently, Moore and Ruska[5] have described the capillaries and small arteries of the heart and skeletal muscle. They found cristae at the junctions between endothelial cells, which they identified with the terminal bars seen with the light microscope. They observed the intracytoplasmic vesicles described by Palade, and found such vesicles peripherally located in the fibers of cardiac muscle, skeletal muscle, and smooth muscle of the arterioles.

Kisch[3] has described cytoplasmic "villi" projecting inward from the endothelial cells of heart capillaries.

The findings reported in the present communication agree in most respects with those of the workers just mentioned, insofar as vessels from the same organs

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are concerned. However, the capillaries of all the organs previously reported upon are concerned primarily with the exchange of fluid, while those of the skin and subcutis described in this paper are concerned with both the exchange of fluid and the regulation of temperature.

MATERIALS AND METHODS

Two-millimeter punch biopsies of the skin and superficial subcutis of normal Negro and white subjects of both sexes were taken from the abdomen and finger tip. The tissue obtained was cut into 1-mm. cubes after removing the epidermis, and fixed for 4 hours at 1° to 3°C. in 1 per cent osmium tetroxide buffered at pH 7.4 according to the method of Palade.[7] Dehydration was carried out in graded methyl alcohol, after which the blocks were embedded in a prepolymerized mixture of 1 part methyl and 12 parts n-butyl methacrylate. Sections were cut at approximately 1/40 μ with a Porter-Blum microtome, and the sections were observed without removal of methacrylate in an R.C.A. EMU3c electron microscope.

OBSERVATIONS

Most of the blood vessels encountered in the dermis were capillaries, although a few muscular vessels were observed in the deepest part of the dermis. In the subcutis the vessels ranged from capillaries to vessels with up to four layers of smooth muscle.

The Capillaries of the Finger Tip.—In the dermis and subcutis of the finger tip, two distinctive types of capillaries were encountered. One type, found predominantly in the deep subcutis and fatty areas of the superficial subcutis, is similar to those described by Moore and Ruska[5] in other organs. The cytoplasm of the endothelial cells is extremely attenuated when the vessels are dilated, leaving a smooth luminal surface interrupted only by bulges produced by the nuclei (Fig. 3). In the smallest capillaries the cytoplasm of a single cell may completely encircle the lumen. Or, in cross section, the wall may consist of parts of several cells, but seldom is more than one endothelial nucleus present in the section.

The cytoplasm of the capillary endothelium contains numerous vesicles ranging from 500 Å to 700 Å in diameter. Such vesicles are found throughout the cytoplasm, but they are mainly in alignment against the cytoplasmic membrane (Fig. 3). Some of them open to the exterior as though they were invaginations of the cytoplasmic membrane. These are undoubtedly the same type of vesicles shown by Palade[8] and Moore and Ruska.[5]

The second type of capillaries in the dermis and subcutis comprises vessels in the same size range as those just described, but the endothelium is distinctive. The endothelium is never as flattened as that in the first type of capillaries, but even in the most dilated ones observed the cytoplasm tapers off evenly from the nuclei to the edges of the cells. When these capillaries are contracted, the endothelial cells are pyramidal in shape, thus narrowing or completely closing the lumens while retaining an even cellular contour (Fig. 5). In cross sections of even the smallest of these capillaries, at least two nuclei usually are seen, and often as many as five or six (Figs. 4, 5, and 6). Filamentous or blunt cytoplasmic processes often project into the lumens (Figs. 6 and 8).

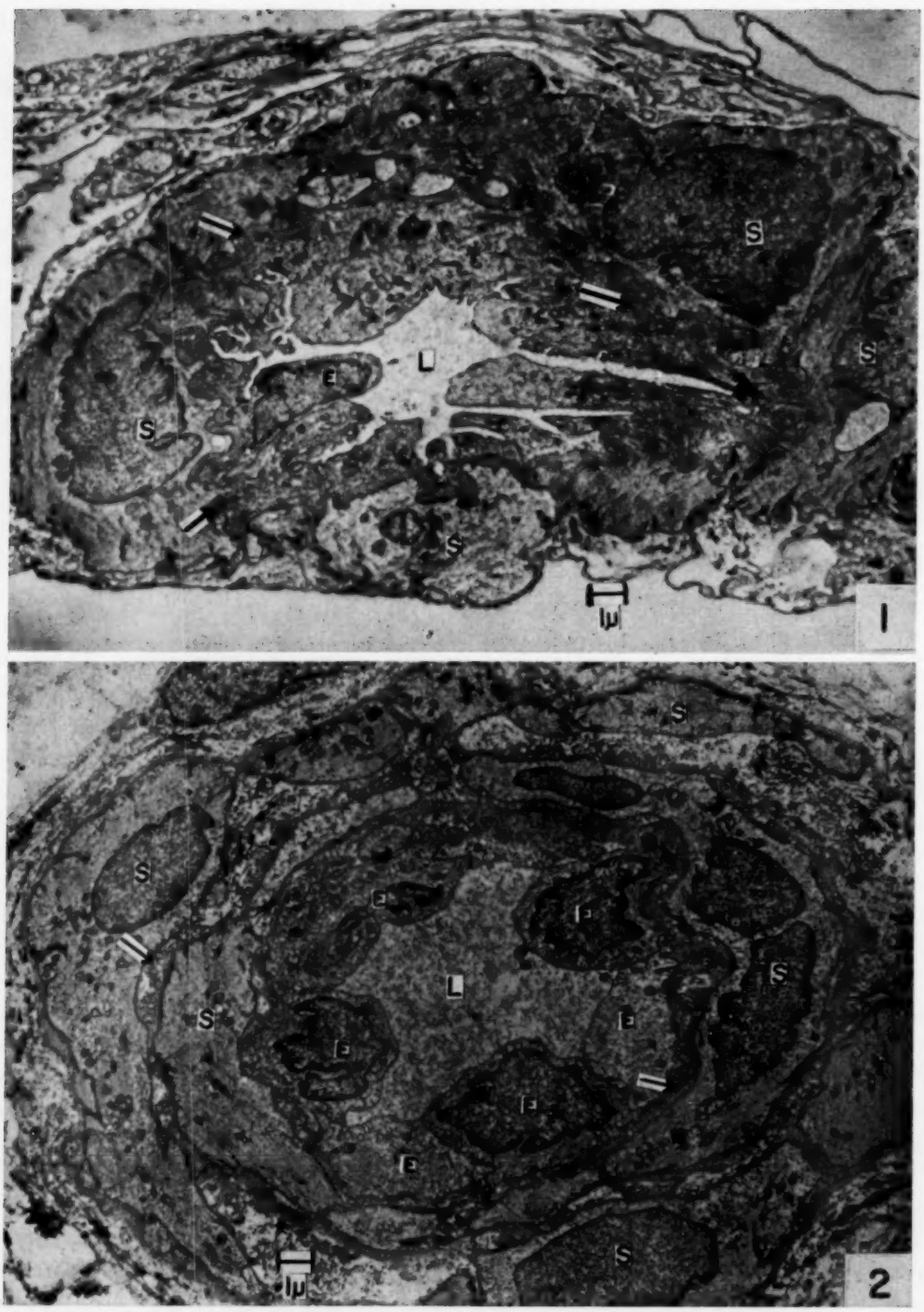
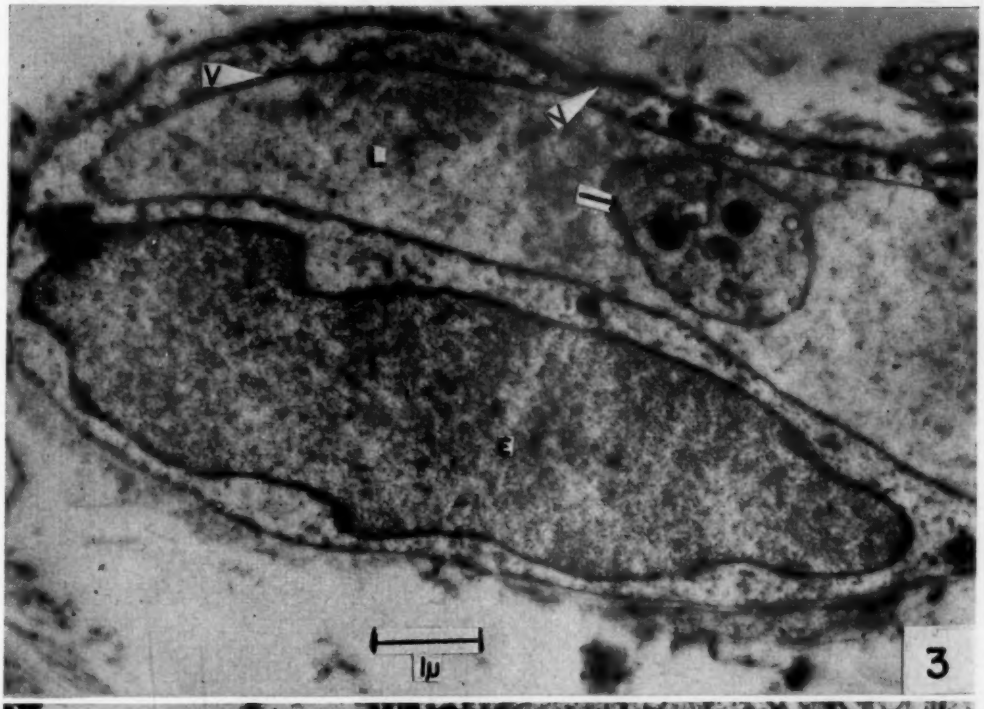


Fig. 1.—A cross section of an arteriole of the ordinary type. Note the prominent internal elastic lamina (arrows) and folded endothelium. *S*, Smooth muscle cell. *E*, Endothelial cell. *L*, Lumen of vessel.

Fig. 2.—Arteriole of the subcutis of the finger tip. Note the thick, almost cuboidal endothelium. No internal elastic lamina is present, but a feltwork of very fine filaments (arrows) and a few collagenous fibers can be seen between the smooth muscle cells and the endothelium and also between adjacent smooth muscle cells. *S*, Smooth muscle cell. *E*, Endothelial cell. *L*, Lumen of vessel.



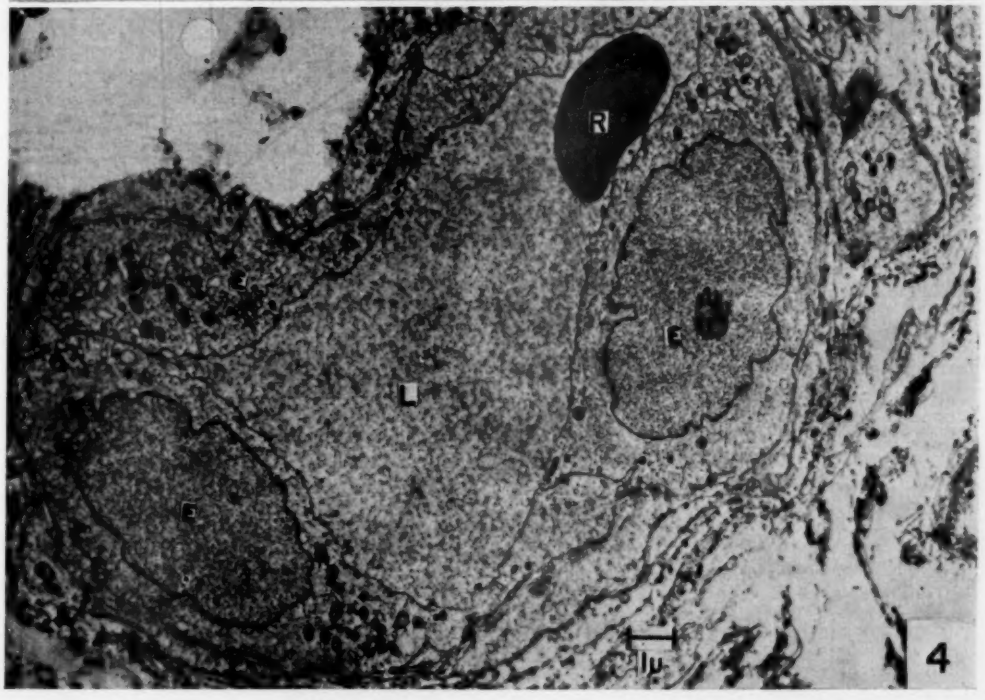
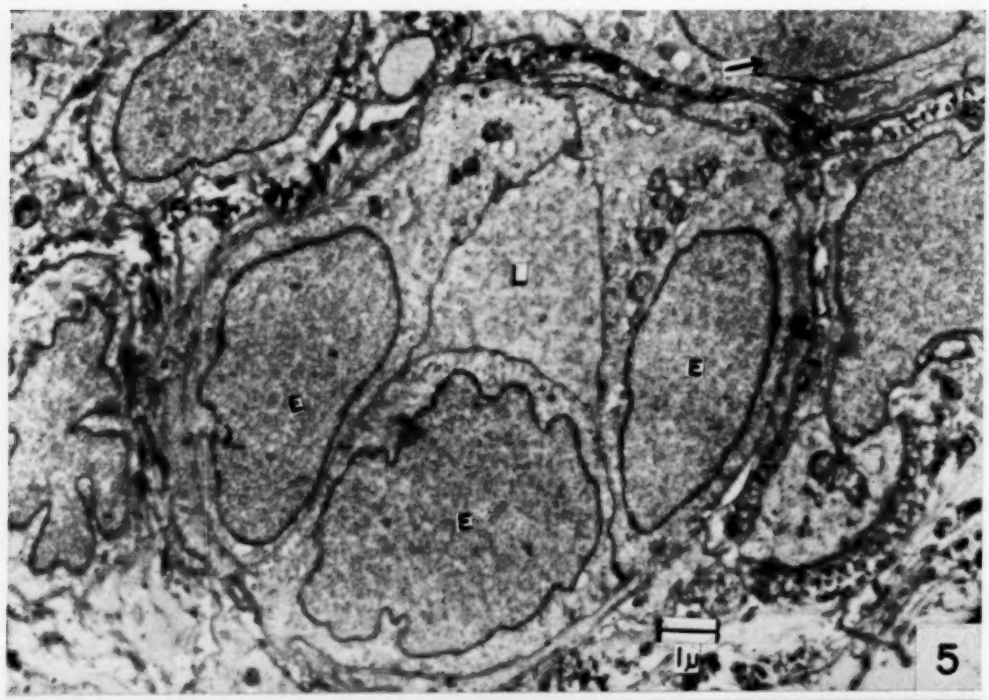


Fig. 3.—A dilated capillary of the ordinary type from a fatty area of the subcutis. Note the attenuated cytoplasm and the numerous vesicles lining the cytoplasmic membrane and scattered in the cytoplasm. The body in the lumen (arrow) is part of a leukocyte. *E*, Endothelial cell. *L*, Lumen of vessel. *V*, Vesicles.

Fig. 4.—Dilated capillary from the region near a sweat gland. Note the thick endothelial cells. Cytoplasmic filaments are not prominent at this magnification. *E*, Endothelial cell. *L*, Lumen of vessel. *R*, Red blood cell.



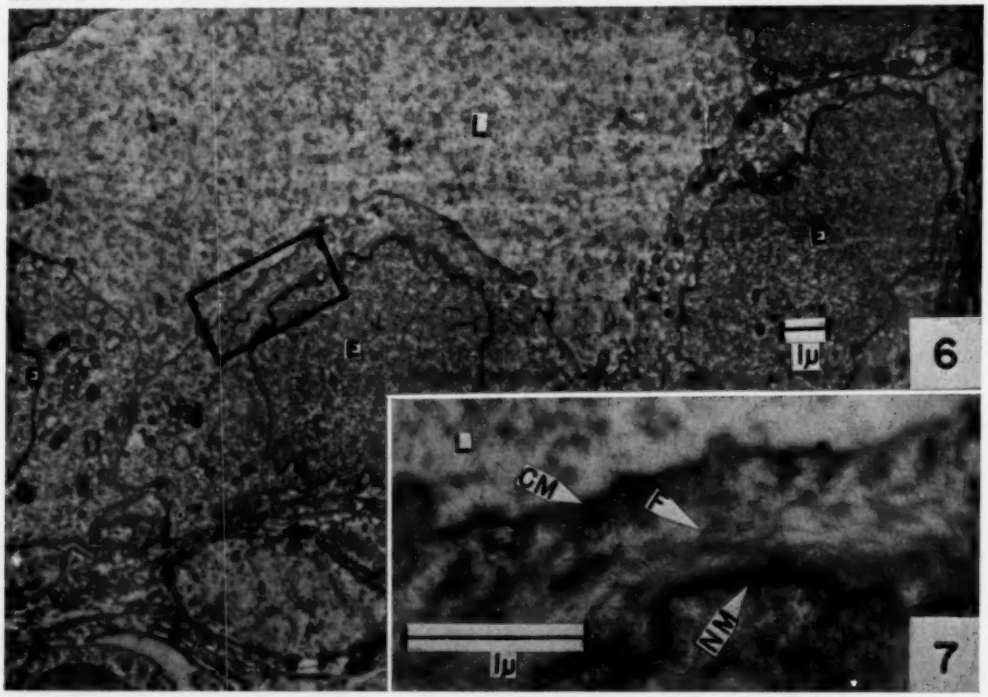
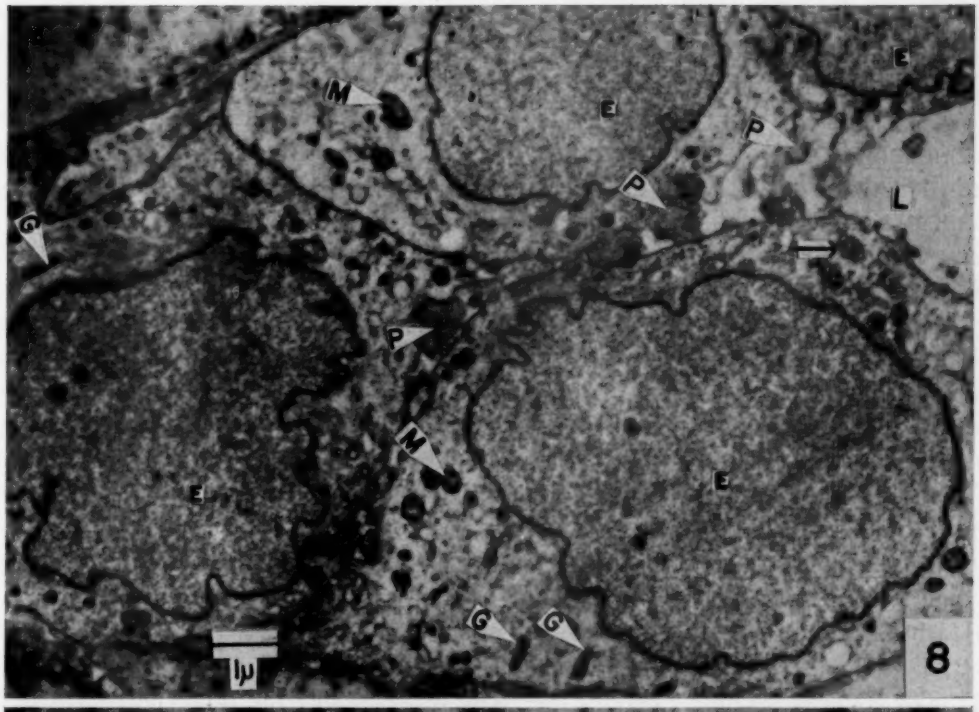


Fig. 5.—A partially contracted capillary near a sweat gland. Notice the thickened, almost cuboidal endothelial cells, and the small lumen. Arrow indicates a cell of the periphery of a sweat gland. *E*, Endothelial cell. *L*, Lumen of vessel.

Fig. 6.—A portion of the wall of a large capillary or small venule from near a sweat gland. Processes can be seen on the luminal surfaces of the pyramid-shaped endothelial cells. *E*, Endothelial cell. *L*, Lumen of vessel.

Fig. 7.—High magnification of the area outlined in Fig. 6, showing the bundles of cytoplasmic filaments. *L*, Lumen of vessel. *CM*, Cell membrane. *NM*, Nuclear membrane.



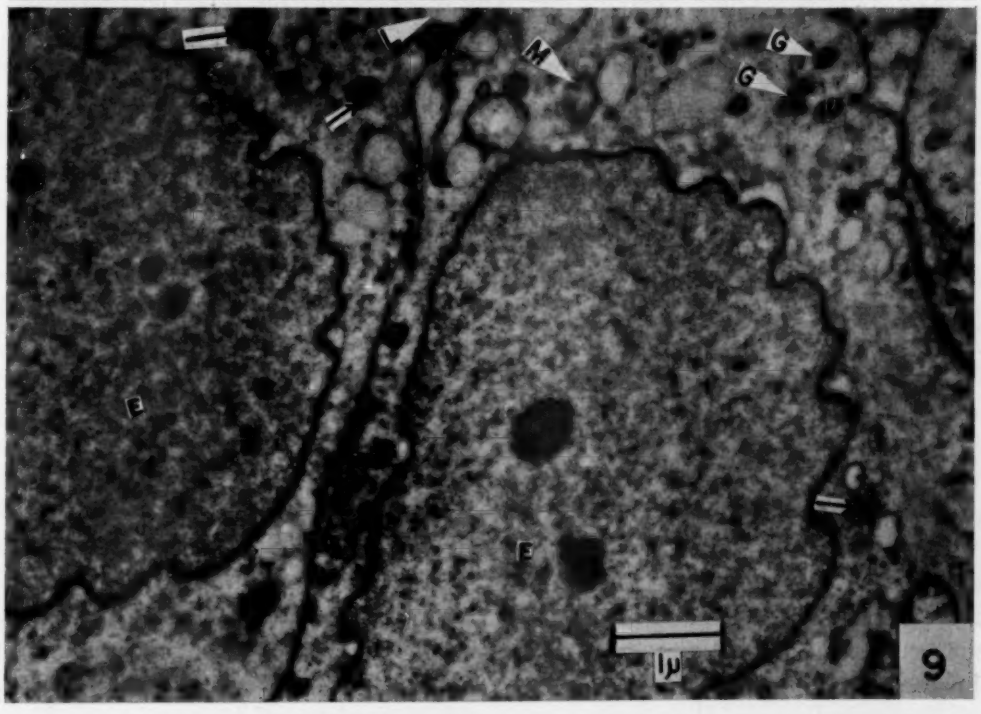


Fig. 8.—A portion of the wall of a capillary from near a sweat gland, showing the dense, rod-shaped granules and processes from the luminal surface of the endothelial cell. Arrow indicates a group of small vesicles enclosed by a membrane. *E*, Endothelial nucleus. *M*, Mitochondrion. *P*, Process on the surface of the cell. *G*, Dense, rod-shaped granule. *L*, Lumen of vessel.

Fig. 9.—An endothelial cell from near a sweat gland, showing cytoplasmic details. Arrows indicate groups of vesicles, each group enclosed by a membrane. *E*, Endothelial nucleus. *M*, Mitochondrion. *L*, Lumen of vessel. *G*, Rod-shaped granules (some in cross section).

These cells also exhibit an internal morphology different from ordinary endothelial cells. In addition to its ordinary elements, the cytoplasm presents large bundles of fine filaments, usually coursing parallel to the nuclear membrane (Figs. 6 and 7). Each of these filaments is approximately 70 Å in diameter. Large bundles of filaments such as these have never been encountered in ordinary endothelial cells, although a few scattered filaments are occasionally present.

In most of these cells, groups of very dense, rod-shaped granules, varying from 0.1 to 0.3 μ in diameter and 0.3 to 0.6 μ in length, are found (Figs. 8 and 9). The significance of these granules is not known.

Scattered in the cytoplasm of many of these cells are small vesicular bodies which so far have not been identified. They appear as groups of closely packed, small vesicles about 400 Å in diameter, each group enclosed by a membrane. The over-all diameter of these bodies is about 0.5 μ (Figs. 8 and 9). Although they are of about the same size as many mitochondria, it is doubted that they are mitochondria; none of the recognizable mitochondria contain any of these vesicles, and none of these bodies contain cristae.

Small intracytoplasmic "pinocytotic" vesicles like those in the cells of ordinary capillaries are not prominent. Small numbers have been encountered just under the cytoplasmic membranes of some cells, but few are scattered in the cytoplasm.

The Arterioles of the Finger Tip.—The arterioles of the finger tip also can be divided into two types on the basis of morphology. One type, found mainly in the deep subcutis, is indistinguishable from the arterioles found in most other organs. The lining cells are flattened when the vessels are dilated, but when the vessels are contracted, the luminal surfaces of the lining cells are convoluted, leaving thin folds of cytoplasm protruding into the lumens (Fig. 1). The nuclei, surrounded by thin rims of cytoplasm, protrude into the lumens in a similar manner. The cytoplasm of the lining cells contains numerous "pinocytotic" vesicles such as those in the endothelium of the first type of capillaries described.

Separating the endothelium from the muscular tunica media is an elastic lamina of 0.1 to 0.3 μ in thickness. The media is composed of one or more layers of smooth muscle cells, the innermost ones lying in close contact with the elastic lamina.

Arterioles of a second type, most of which are found superficial to those just described, are present in large numbers in the dermis and subcutis of the finger tip. The lining cells of these vessels closely resemble the thick, filament-containing cells described above. When dilated vessels of this type are seen in cross section, one of the most striking features is the large number of endothelial nuclei present for the size of the vessel. In contracted arterioles these endothelial cells assume pyramidal or columnar shapes, always retaining the smooth, general contour of their free borders.

The cytoplasm of these cells contains the same type of filaments, rod-shaped granules, and vesicular bodies described earlier; however, the granules and vesicular bodies are fewer in number than in capillary endothelium. Intracytoplasmic vesicles are less frequent than in ordinary endothelium but have the same distribution.

No elastic lamina has been observed in any arterioles of this type. The smooth muscle cells are separated from the endothelium and from each other by rather thick layers of connective tissue. Some collagenous fibers can be identified, but this connective tissue appears to consist mainly of a feltwork of extremely delicate fibrils whose composition has not been determined (Fig. 1).

The Capillaries and Arterioles of the Dermis and Subcutis of the Abdomen.—The capillaries and arterioles of the abdominal dermis and subcutis are of the same types as those found in the finger tip. Many of the vessels lined by the thick, filament-containing endothelial cells are associated with the sweat glands in this region, as they were in the finger tip. Since sweat glands are less numerous here, these vessels are also somewhat less numerous.

Venules.—Small venules are difficult to identify with certainty unless at least part of a smooth muscle cell is present in the section. It is therefore being assumed that all vessels that cannot be recognized as arterioles, if more than 15 μ in diameter, are venules rather than capillaries, even though no smooth muscle is present in a particular section.

Most of the venules are lined by the same type of thick, filament-containing endothelial cells described in conjunction with arterioles and capillaries. These cells are usually pyramidal in shape, with their apices toward the lumens. All contain large bundles of filaments, and many contain rod-shaped granules and vesicular bodies like those in capillaries.

Just external to the basement membrane is usually found a densely packed sheet of collagenous fibers and occasional fragments of smooth muscle cells.

DISCUSSION

Some variation in the structure of capillaries and arterioles normally occurs from one organ to another, and even among vessels of the same organ; but no such striking variation as that in the vessels of the dermis and subcutis has been observed previously. It is recognized that the endothelium of some vessels which permit the passage through their walls of large amounts of fluid contains many pores (renal glomeruli and the peritubular capillaries). Another specialization occurs in the capillaries of the pulmonary alveoli, where the cytoplasm is extremely attenuated.

The function of the small vessels of the dermis and subcutis is somewhat specialized, since in addition to the exchange of fluid, these vessels aid in the regulation of temperature, which requires rapid contraction and dilation. It seems reasonable that these vessels also would show some structural differences related to their special activities.

The observations reported here support this assumption to a certain extent. Two distinctive types of capillaries have been shown to exist in dermis and subcutis. The ordinary thin-walled capillaries are found predominantly in the more fatty areas, and occasionally among the dense bundles of collagenous fibers of the dermis. They closely resemble the capillaries found in muscle, pancreas, and many other organs—capillaries whose predominant function is apparently the exchange of fluid. It seems therefore that these capillaries in skin and subcutis might have the same prime function.

Capillaries composed of the thick, filament-containing cells would be expected to have a different function. It is evidently not so simple as this, since such vessels make up the capillary network around the secretory portions of the sweat glands, where there is also a great need for the exchange of fluid.

The ability of small vessels to contract is necessary for the regulation of temperature, and this ability is known to be well developed in at least some of the subcutaneous vessels. The numerous cytoplasmic filaments present in these endothelial cells, and the rounded appearance of the cells in the constricted vessels suggest that they are actively contractile. The properties of such cells in arterioles and venules would effect a rapid and complete closure of these vessels.

It is difficult to see how such thick cells could be so active in the exchange of fluid if intracytoplasmic vesicles are of major importance in this process, as Moore and Ruska believe. It appears unlikely, in view of their scarcity, that the vesicles in these particular vessels have an important role in the exchange of fluid.

The relationship between the vessels discussed here and the glomus bodies or arteriovenous shunts of the finger tip is so far unknown, since no recognizable glomus bodies or shunts have yet been encountered.

SUMMARY

Observations have been made on the small blood vessels of the dermis and subcutis of the human finger tip and abdomen. Two types of vessels have been described—vessels which closely resemble those of most other organs, and a second type of vessel never before reported. Vessels of the second type are found predominantly in the vicinity of sweat glands, and are lined by endothelial cells with the following characteristics: (1) small, dense, rod-shaped granules in the cytoplasm; (2) large bundles of very fine filaments in the cytoplasm; (3) groups of small vesicles in the cytoplasm, each group enclosed by a membrane; (4) thicker than typical endothelium, the cells in contracted vessels being pyramidal or columnar in shape.

A possible functional signficance of this specialized endothelium has been suggested.

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Paroxysmal Supraventricular Tachycardias Complicating Organic Heart Disease

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The paroxysmal supraventricular tachycardias have been generally considered to be benign, well-tolerated mechanism disorders, occurring usually in otherwise normal individuals. Yet it has been our clinical impression, in a hospital practice, that such mechanism disorders also occur commonly in patients with diseased hearts. Furthermore, we have observed in such patients a conspicuous refractoriness to the usual methods of therapy and, consequently, a more serious course and a poor prognosis.

There is a relative paucity of detailed information concerning the incidence, therapeutic response, and the prognosis of paroxysmal supraventricular tachycardias in patients with organic heart disease. Therefore, we have considered it timely to review the clinical and electrocardiographic data accumulated in the past 15 years in 175 consecutive patients with paroxysmal supraventricular tachycardia treated in the University of Texas Hospitals.

CRITERIA

The prerequisite for inclusion in this study was electrocardiographic identification of a dominant ectopic pacemaker, either atrial or nodal, and one of the reliable criteria of organic heart disease. However, because of electrocardiographic similarities among certain of the supraventricular arrhythmias, additional clinical criteria were at times necessary to establish the diagnosis. The criteria that have been established will be presented below.[1-6]

Paroxysmal atrial or nodal tachycardia with 1:1 conduction at moderately rapid rates of 150 to 200 per minute usually offered little difficulty in diagnosis, since the electrocardiograms showed: (1) an occasionally recorded or clinically

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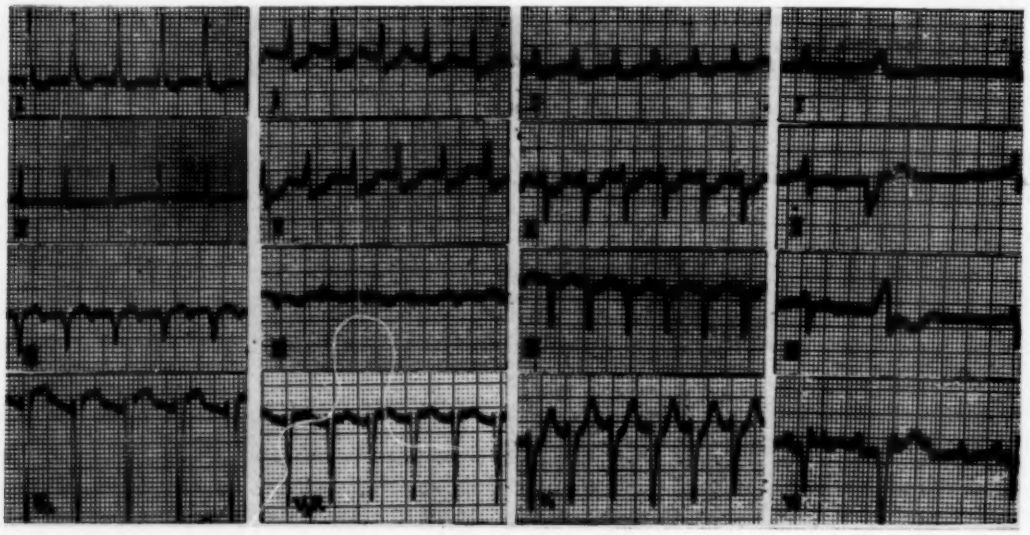
noted abrupt onset or offset; (2) an almost absolute regularity in minute-to-minute counts of the rate; (3) the presence of identifiable P waves in one or more leads.

Absolute identification of P waves in the electrocardiogram was at times impossible, because of their superimposition upon the QRS complex or T wave (see Fig. 1,*C*). In these instances a diagnosis of supraventricular tachycardia of indeterminate type was made when the remainder of the clinical and electrocardiographic criteria were demonstrable or present.[4] Definite P waves may be revealed in the precordial leads over the atria in the second right intercostal space or in the esophageal leads, under the above circumstances.



A. *B.* *C.* *D.*

Fig. 1.—The four common types of paroxysmal supraventricular tachycardia in ECG Leads I, II, III, and V_2, V_2R, or V_1. *A*, Atrial tachycardia (30 patients). *B*, Nodal tachycardia (40 patients). *C*, Indeterminate tachycardia (11 patients). *D*, Atrial tachycardia with A-V block (45 patients).

The response to carotid sinus pressure was frequently an aid in diagnosis (Fig. 2).[5] The typical "all or none" response of the paroxysmal supraventricular tachycardias with 1:1 conduction to carotid sinus pressure is characteristic, because there is either abrupt reversion to sinus rhythm or no demonstrable effect (Fig. 2,*B*). Transient slowing of the rapid pacemaker in sinus tachycardia by carotid sinus pressure, when demonstrable, was helpful in excluding an ectopic tachycardia (Fig. 2,*A*). In this series, atrial tachycardias at relatively slow rates were included only when abrupt reversion to normal rhythm by the usual methods of therapy proved them to be ectopic in origin.

In atrial flutter, carotid sinus pressure frequently produces a transient increase in A-V block, allowing the identification of the constantly undulating flutter "c" waves (Fig. 2,*C*). Differentiation between paroxysmal tachycardia with atrioventricular block and slow atrial flutter was difficult when the rate of the ectopic pacemaker was in the range of 200 to 250 per minute. There might be a similar response to vagal stimulation, producing a transient increase

in the atrioventricular block and, consequently, a similar slowing of the ventricular rate (Fig. 2,*C* and *D*). Other criteria were then necessary for correct interpretation. The most valuable electrocardiographic sign is the identification of the undulating base-line or "sawtooth" configuration in one or more leads in atrial flutter, in contrast to an isoelectric base line of 0.04 second, or more, in every lead in the paroxysmal tachycardias.

In addition, the clinical suspicion of digitalis intoxication and/or depletion of potassium definitely favored the diagnosis of paroxysmal tachycardia with partial A-V block in a few instances.[6] The response to small test doses of a rapidly acting digitalis preparation, deslanoside D, 0.4 mg. intravenously, established the true nature of the disorder by slowing the ventricular rate in atrial flutter, or by producing more conspicuous evidence of digitalis intoxication in paroxysmal tachycardia with atrioventricular block.

Patients in whom paroxysmal supraventricular tachycardia was of a transient nature were excluded from the study. In most of the cases the ectopic rhythm was constant in each lead during the routine electrocardiogram. In a few instances in which there was intermittent resumption of sinus rhythm, the ectopic rhythm was dominant over a clinically observable period of time varying from several minutes to several hours or several days.

INCIDENCE

Table I summarizes the underlying cardiac status in the 175 cases with paroxysmal supraventricular tachycardia. There were 44 patients (25 per cent) without evidences of heart disease, of whom 17 manifested serious systemic (noncardiac) disease, and 8 others showed the accelerated conduction WPW syndrome. There were 131 patients (75 per cent) who showed definite evidences of pre-existing organic heart disease. Included in this group were 45 patients in whom the disorder was complicated by second or third degree atrioventricular block, and 5 who showed an associated WPW syndrome.

It must be pointed out that most of our patients were hospitalized for therapy of serious underlying diseases. In the general population the incidence of the paroxysmal supraventricular tachycardias in patients with organic disease is obviously much lower than our records would indicate.

TABLE I. UNDERLYING CARDIAC STATUS IN THE 175 PATIENTS

Normal Heart		44	(25%)
No discernible organic disease	19		
Serious noncardiac disease present	17		
Wolff-Parkinson-White syndrome	8		
Organic Heart Disease		131	(75%)
Tachycardias without A-V block	81		
Tachycardias with A-V block	45		
Wolff-Parkinson-White syndrome	5		
Total Cases		175	

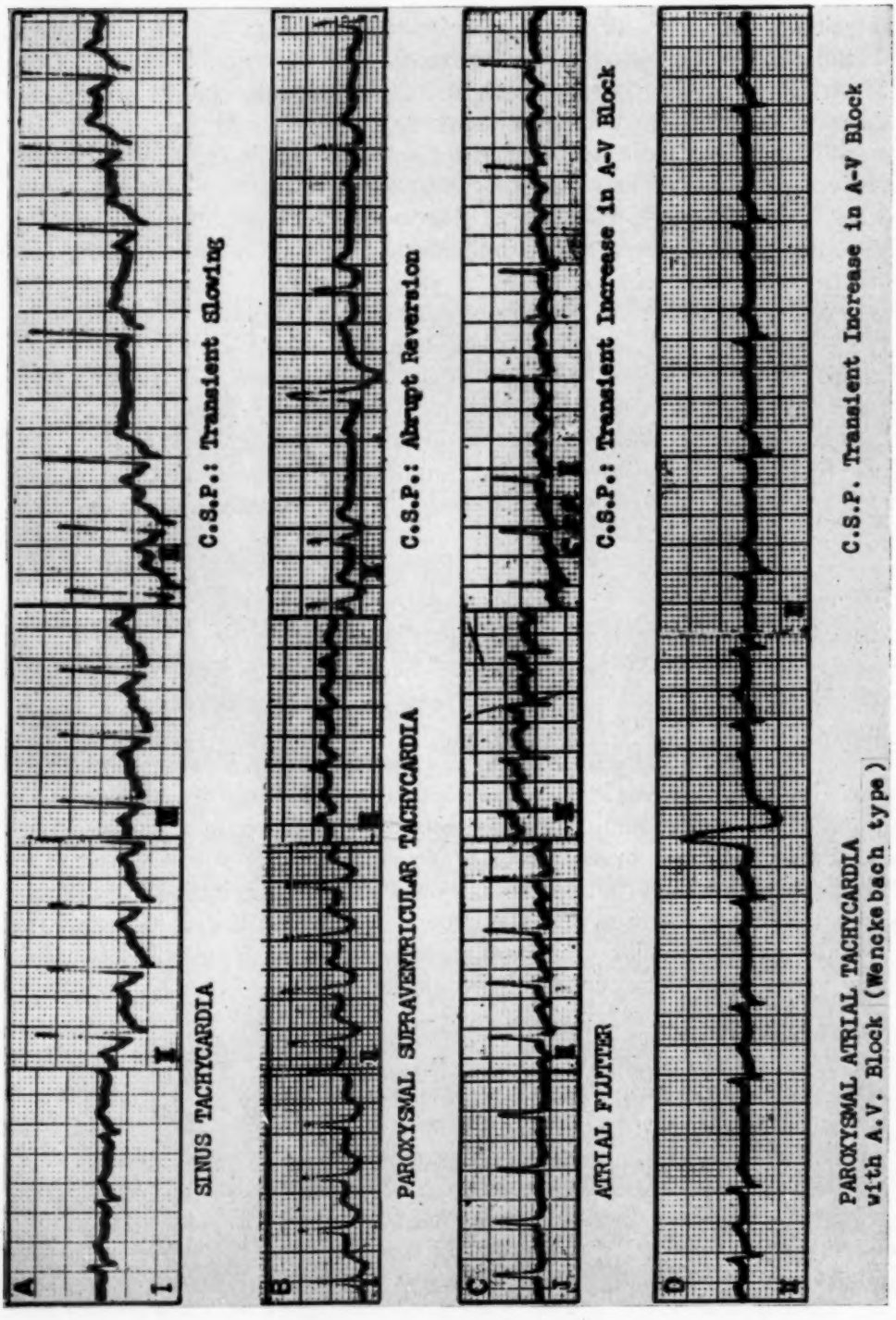


Fig. 2.—Supraventricular tachycardias of various types are on the left, with the effect of indirect vagus stimulation by carotid sinus pressure (C.S.P.) on the right. *A*, Sinus. *B*, Paroxysmal. *C*, Slow atrial flutter. *D*, Paroxysmal with A-V block.

The age distribution of the patients in relation to cardiac status is summarized in Fig. 3. The peak incidence of patients with normal hearts was in the age group from 41 to 50 years, while that of patients with organic heart disease was in a higher age group, from 50 to 70 years.

Of the 44 patients with normal hearts there were 21 males and 23 females. Of the 131 patients with organic heart disease there were 62 males and 69 females. Thus, the distribution between the sexes was approximately equal in both groups.

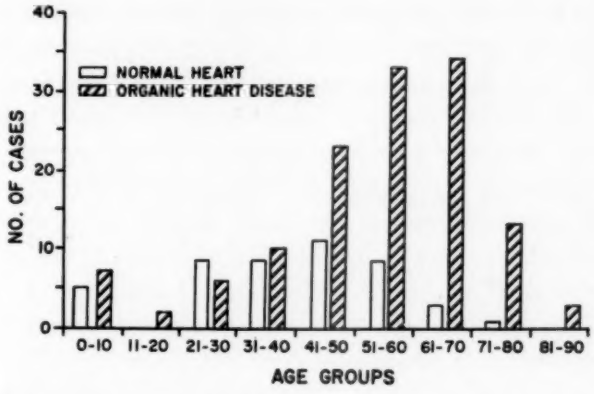


Fig. 3.—Distribution of 175 consecutive cases of paroxysmal supraventricular tachycardia according to age groups and as to whether the patient had a normal heart or organic heart disease.

ETIOLOGY

The etiology of the organic heart disease in the 131 patients in whom paroxysmal supraventricular tachycardia was observed is summarized in Table II. Atheromatous coronary artery disease and systemic hypertension, either alone or in combination, were present in 88 (67 per cent) of the patients with organic heart disease. Recent myocardial infarction had occurred in 9 patients, and was confirmed at autopsy in 3. Rheumatic heart disease was present in only 9 patients (7 per cent), and its low incidence as compared to that of a previous report[7] is probably due to its relative infrequency in this area in comparison to the northern and eastern United States.[8] Cases of heart disease of pulmonary, syphilitic, congenital, and hyperthyroid origin were observed only occasionally.

Complicating systemic disorders which predisposed to myocardial irritability in several of the patients with organic heart disease were anemia, infection, and uremia. Widespread malignancy was present in 14 patients. There were 10 patients in whom the tachycardia appeared during the immediate postoperative period, and presumably was related to the attendant physical or psychologic stress[9] or to disturbances in electrolytes. The latter, particularly hypopotassemia, was also implicated in an occasional patient with serious systemic noncardiac disease. Recurring episodes could be associated in 2 patients with hypopotassemia secondary to the administration of cortisone for drug sensitivity.

Digitalis intoxication was the major precipitating factor in two thirds of the 45 patients manifesting atrioventricular block, but could be incriminated

in only 5 of the 81 cases with 1:1 atrioventricular conduction. Since all of the electrocardiograms showing atrioventricular block were obtained in patients with organic heart disease, this would confirm previous observations from this Clinic[10] that serious myocardial damage in combination with digitalis intoxication are the usual prerequisites for the occurrence of paroxysmal supraventricular tachycardia with atrioventricular block, and that the prognosis is, consequently, made truly serious by the complicating A-V block.

TABLE II. ETIOLOGY OF ORGANIC HEART DISEASE

TYPE OF HEART DISEASE	NUMBER OF PATIENTS
Arteriosclerotic	49
Hypertensive	11
Arteriosclerotic and Hypertensive	28
Recent Myocardial Infarction	(9)
Rheumatic	9
Pulmonary	8
Syphilitic	3
Congenital	7
Hyperthyroid	4
Miscellaneous	12
Total	131

SYMPTOMS AND SIGNS

An analysis of the symptoms and signs related to the arrhythmia showed the clinical manifestations to vary from palpitation, weakness, and exertional dyspnea to the more serious chest pain, shock, and congestive failure (Table III).

TABLE III. SYMPTOMS AND SIGNS

SYMPTOM OR SIGN	NORMAL HEART (44)	ORGANIC HEART DISEASE (131)
Breathlessness and/or weakness as the sole manifestation	16 (36%)	22 (17%)
Chest Pain	1 (2%)	19 (15%)
Shock	3 (7%)	35 (27%)
Heart Failure as a new manifestation	3 (7%)	21 (23%)
Heart Failure present before onset of tachycardia	———	41 (31%)

Palpitation was noted by most of the patients. Dyspnea or weakness on exertion as the only additional symptoms in 36 per cent of the patients with normal hearts was due possibly to psychogenic overlay, since it was present in only 17 per cent of the patients with organic heart disease, who usually also had other, more alarming manifestations. Chest pain was present in only one patient showing

no evidence of organic heart disease, and this patient's ventricular rate was 207 per minute. In contrast, chest pain was a complaint of 19 patients (15 per cent) with organic heart disease. However, it was secondary to myocardial infarction in 5 of these, and to dissecting aneurysm of the aorta in another. Chest pain was common in patients with severe coronary heart disease, but could be correlated with the rapidity of the ventricular rate only in those patients who had no evidence of serious coronary heart disease. In such patients it was occasionally noted when the ventricular rates exceeded 180 per minute.

Shock and heart failure were associated with the tachycardia in patients without evidences of organic heart disease only when the underlying noncardiac illness, infection, anemia, or malignancy was most severe. In such instances the tachycardia was often a terminal event. Shock and congestive heart failure were frequent complications of the tachycardia in organic heart disease; each was present as a new finding in approximately one fourth of the cases. In thirty-one per cent of the patients with damaged hearts there had been pre-existing congestive heart failure, and it was usually much aggravated when the ventricular rates were rapid. Heart failure occurred in 2 infants with ventricular rates of 210 and 256 per minute, in the presence of severe infection, and in one 50-year-old adult with ventricular rates of 160 per minute, in the presence of widespread pneumonia and carcinoma of the stomach.

OTHER ELECTROCARDIOGRAPHIC FINDINGS

Electrocardiograms were available and analyzed in all cases. The types of supraventricular tachycardias are illustrated in Fig. 1, the legend of which lists the number of organic heart disease cases of each type. The WPW syndrome was diagnosed in 13 patients of the entire series, and these were excluded from further study because they form a special group. In the remaining 126 patients with heart disease, evidence of recent or old myocardial infarctions, ventricular hypertrophies, pre-existing bundle branch block, and primary or secondary ST-T wave changes were frequent findings. Functional bundle branch block or aberration of the QRS complex during the tachycardia was observed in 6 patients with organic heart disease, but it was also of similar incidence in patients with normal hearts. Thus, this finding in association with a rapid ventricular rate could not be interpreted as an electrocardiographic sign of latent myocardial pathology.

The atrial rates during the tachycardia were analyzed in each major group of patients, and are summarized in Table IV. This table indicates the number of cases in each range of atrial rates for three groups of patients—those with normal hearts, those with organic heart disease and 1:1 conduction, and those with organic heart disease and second or third degree atrioventricular block. The percentages indicate the distribution of cases in the usual range and above. While the majority showed atrial rates in the usual range of 150 to 200 per minute, the tracings with second or third degree A-V block often exhibited atrial rates in the higher range of 200 per minute and above. This presumably is the result of increased myocardial irritability, frequently induced by digitalis intoxication,

and emphasized the necessity of a careful clinical evaluation in distinguishing this type of arrhythmia from slow atrial flutter.[5,11]

TABLE IV. ATRIAL RATES IN PAROXYSMAL SUPRAVENTRICULAR TACHYCARDIA

ATRIAL RATE (PER MINUTE)	NORMAL HEART (NUMBER OF PATIENTS)		ORGANIC HEART DISEASE			
			TACHYCARDIA WITHOUT A-V BLOCK (NUMBER OF PATIENTS)		TACHYCARDIA WITH A-V BLOCK (NUMBER OF PATIENTS)	
100–109						
110–119			1		1	
120–129						
130–139	2		2		1	
140–149	3		7		1	
150–159	1		6		3	
160–169	6		16		8	
170–179	8	56%	13	74%	4	60%
180–189	5		17		5	
190–199	1		8		7	
200–209	2		3		4	
210–219	4		2		6	
220–229	2		3		2	
230–239		28%	1	14%	2	33%
240–249	1		1		1	
250–259	1		1			
Totals	36		81		45	

TREATMENT

When an appraisal was made of the value of various methods of therapy, the patients with 1:1 conduction were considered separately from those showing increased degrees of A-V block. Table V summarizes the results of therapy of supraventricular tachycardia with 1:1 conduction in 27 patients with normal hearts and in 48 patients with organic heart disease. Carotid sinus pressure or its equivalent (ocular pressure, Valsalva or Mueller maneuver), potentiated at times with Prostigmin, was effective in 13 of 18 patients with normal hearts, but succeeded in reversion to sinus rhythm in only 9 of 24 patients with organic heart disease. Actually, the percentage of success with such measures in patients with organic heart disease was even less, since only those patients were included in the calculations whose records showed that this procedure was attempted (Table V). Other therapy was administered only if these simple procedures proved ineffective. In such situations, digitalis was effective in both groups, achieving success in 87 per cent of trials in normal hearts, and in 75 per cent in diseased hearts. Digitalis was withheld from patients in whom it may have been a precipitating factor, particularly if there was any hint of a depletion of potassium. Potassium salts were effective in 3 cases with clinical evidences of a significant deficit of potassium (Fig. 4). Quinidine, used less frequently, was effective in 50 per cent of trials in normal hearts and in 67 per cent in diseased

hearts. There was a comparable incidence of spontaneous reversion in both groups. Patients with pre-existing cardiac disease exhibited a higher percentage of treatment failures, accounting in part for the somewhat more serious prognosis in this group.

TABLE V. THERAPEUTIC RESULTS IN SUPRAVENTRICULAR TACHYCARDIA WITH 1:1 CONDUCTION: METHOD OF REVERSION IN SINGLE EPISODES

METHOD	NORMAL HEART (27 PATIENTS)		ORGANIC HEART DISEASE (48 PATIENTS)	
	NUMBER OF CASES		NUMBER OF CASES	
	TRIED IN	EFFECTIVE IN	TRIED IN	EFFECTIVE IN
C.S.P.* and/or Prostigmin	18	13 (72%)	24	9 (37%)
Digitalis	7	6 (87%)	24	18 (75%)
Quinidine	4	2 (50%)	9	6 (67%)
Vasopressors	—	—	1	1
Potassium Salts	1	1	2	2
Spontaneous reversion		4 (13%)		8 (13%)
Failure of response to drugs		1 (3%)		4 (7%)

*Carotid Sinus Pressure.

PROPHYLACTIC THERAPY

There were 20 patients in this series who had repeated episodes of paroxysmal tachycardia not due to digitalis during the period of observation. Table VI summarizes the results of prophylactic drug therapy in this group. Digitalis was highly effective in the prevention of recurrences, while quinidine, in a wide range of dosages, was much less useful in prophylaxis than in the reversion of single episodes. Procaine amide (Pronestyl) was successful in one patient who had repeated attacks on maintenance therapy with digitalis and quinidine. Three patients with frequent attacks complicating organic heart disease did not respond to any prophylactic drug therapy employed.

TABLE VI. PREVENTION OF RECURRENCES IN PATIENTS WITH FREQUENT ATTACKS OF PAROXYSMAL TACHYCARDIA

DRUG USED	NORMAL HEART (3 PATIENTS)		ORGANIC HEART DISEASE (17 PATIENTS)	
	TRIED IN	EFFECTIVE IN	TRIED IN	EFFECTIVE IN
Digitalis	1	1	12	9 (75%)
Quinidine	2	2	11	4 (36%)
Procaine amide	–	–	1	1
Failure of response to drugs				3 (18%)

The reversion of paroxysmal tachycardia with atrioventricular block is a special therapeutic problem. This type of disorder is almost always associated with severe cardiac disability, and, as noted earlier, was precipitated by digitalis intoxication in two thirds of our cases. A previous study by Herrmann, Decherd and Schwab[10] focused attention on the role of digitalis in the genesis of this arrhythmia, and in recent years the important influence of the depletion of potassium as an underlying factor has been emphasized.[6,11] Since both digitalis and a low concentration of potassium increase myocardial irritability, it is not surprising to find many instances of paroxysmal tachycardias in patients on maintenance digitalis therapy, especially after mercurial and carbonic anhydrase inhibitor diuretics have produced an even greater loss of potassium. Because of the relatively slow ventricular rate produced by the accompanying block, an arrhythmia may be unsuspected clinically in such patients, and digitalis continued or even increased in dosage.

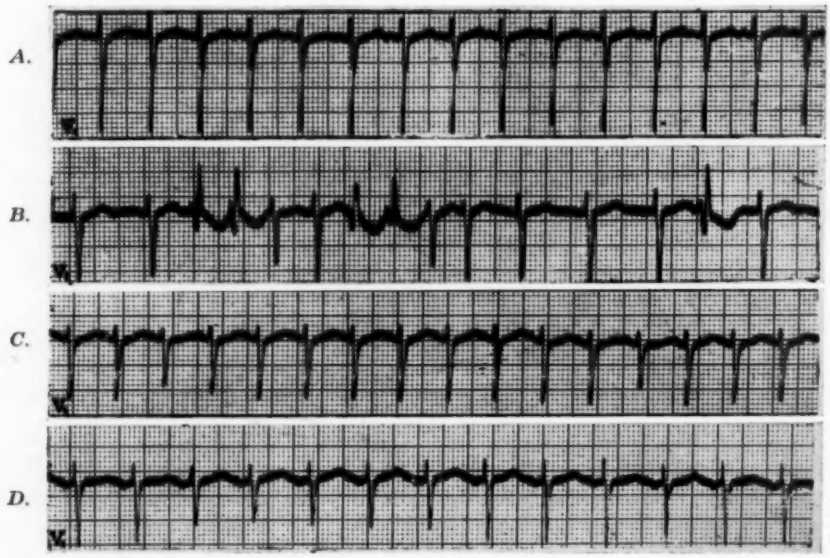


Fig. 4.—Paroxysmal atrial tachycardia in a case of depletion of potassium. *A*, Initially, with 1:1 conduction at a rate of 160 per minute. *B*, Thirty minutes after 0.8 mg. of Cedilanid D, I. V.; varying grades of A-V block and premature ventricular contractions. *C*, After KCl, 80 mEq., I. V. over 14 hours; paroxysmal atrial tachycardia with 1:1 conduction. *D*, After KCl, 100 mEq., I. V. over 15 hours; reversion to normal sinoatrial rhythm.

In 7 of the 30 patients in our study who showed definite, but unrecognized evidence of digitalis intoxication, the drug was continued at the same or increased dosage. All 7 of these patients died within a few days, with the arrhythmia persisting until death. However, of the remaining 23 patients in whom the arrhythmia and its cause were recognized, and from whom digitalis was withdrawn, only 2 died with the arrhythmia unreverted. Administration of potassium salts was especially gratifying, with prompt reversion in 9 of 10 cases (Fig. 4).

Fig. 4 illustrates the effect of therapy in a 69-year-old woman who developed atrial tachycardia as the result of a depletion of potassium in the absence of

digitalis therapy. Initially, the patient manifested an atrial tachycardia with a ventricular rate of 160 per minute. She was given 0.8 mg. of lanatoside (Cedilanid D) intravenously in an attempt to re-establish sinus rhythm. The second tracing shows clearly the hazardous results of even this small amount of digitalis in the presence of a depletion of potassium; varying degrees of A-V block and ventricular irritability consistent with digitalis intoxication appeared. At this point, the true nature of the disorder was obvious, and a dose of 80 mEq. of potassium chloride was given by intravenous infusion. The third tracing shows reversion to an atrial tachycardia with 1:1 conduction, and after an additional 100 mEq. of potassium, conversion to sinus rhythm at a rate of 124 per minute was accomplished. It is important to emphasize this sequence of therapeutic events also in the reversion of a supraventricular tachycardia with A-V block, as pointed out by Lown and Levine.[6] The return of the tachycardia to 1:1 conduction must be understood as an intermediate step in reversion, and not as an adverse effect of therapy. At this point, continued therapy with added potassium salts, procaine amide, or quinidine is indicated in order to accomplish restoration of sinus rhythm.

One child in our series exhibited chronic atrial tachycardia[12] with a varying A-V block over a 2-year period. Digitalis intoxication or depletion of potassium were not present. Quinidine, procaine amide, and potassium salts were ineffective in controlling this disorder. Digitalis, however, induced a higher degree of A-V block, and by lowering the ventricular rate to more normal levels, maintained cardiac compensation.

PROGNOSIS

There was no mortality due to this disorder in patients with normal hearts, and the only deaths occurred in those patients in whom the cause could be attributed to serious underlying systemic or heart disease. Although the disorder could usually be reverted, there was an over-all mortality rate of 40 per cent during the period of observation in the patients with organic heart disease. The mortality rate was 31 per cent in patients with tachycardia and 1:1 conduction, and 47 per cent in those instances where the tachycardia was complicated by higher degrees of A-V block and usually also by digitalis intoxication. In general, this high mortality rate reflects the severity of the underlying cardiac or systemic illness, rather than a direct effect of the tachycardia. There were, however, 7 instances of patients with heart disease with tachycardia and 1:1 conduction, in whom the disorder was felt to be the major factor causing death. This is an immediate mortality rate of 9 per cent in these patients. Eleven of the 45 patients with associated second and third degree A-V block died with the arrhythmia uncontrolled, usually with poorly responsive or unresponsive heart failure, with the frequently added factor of digitalis intoxication.

CASES ASSOCIATED WITH MYOCARDIAL INFARCTION

The association of supraventricular tachycardia with myocardial infarction is regarded by Askey[13] as an ominous sign; there was a mortality of 100 per cent

in his 5 patients. He emphasized the refractoriness of such patients to all methods of therapy.

Supraventricular tachycardia alone in patients with normal hearts, especially in infants and children, can mimic the clinical picture and electrocardiographic changes of myocardial infarction, with chest pain, shock, or heart failure; these cases should therefore be recognized and excluded. There were 9 patients in our series who showed clinical and electrocardiographic evidences of myocardial infarction; confirmation at autopsy was made in 3 of these cases. Three additional patients exhibited myocardial infarctions from the clinical standpoint, but the unequivocal electrocardiographic signs were absent. In the 9 patients with objective evidence of infarction, 6 died during the period of observation. However, reversion to sinus rhythm was accomplished in 6 of these 9 patients, and only 3 died with the disorder uncontrolled. Although the response in our patients was somewhat better than that in Askey's patients, our experiences would confirm his impressions that this disorder complicating myocardial infarction is indeed an ill omen. The prognosis appears to be even more serious than that in paroxysmal ventricular tachycardia.

DISCUSSION

The initial aim of therapy in paroxysmal supraventricular tachycardia is the interruption of the acute attack. In the patient with organic heart disease the development of a rapid ventricular rate may produce serious and alarming signs of coronary insufficiency, shock, or congestive heart failure. In such patients, re-establishment of sinus rhythm is indicated as promptly as possible, and may be lifesaving.

In heart disease cases the tachycardia tends to be refractory to the usual measures for reversal, and attention must be directed to alleviation of the underlying and the precipitating factors. Careful consideration must be given to the possibility of such underlying causes as myocardial infarction, digitalis intoxication, and depletion of potassium.

In all cases the simple corrective measures which result in an increase of vagus tone should be applied first.[14,15] Such procedures include the execution of either the Valsalva or the Mueller maneuver, induced gagging or vomiting, and carotid sinus or ocular pressure.

Prostigmin (neostigmine) 0.5 mg. intramuscularly may in itself revert the arrhythmia, or may successfully potentiate a repeated trial of reflex vagal stimulation.[16]

If the supraventricular tachycardia is refractory to the usual measures that produce an increase in vagal tone, the usual effectiveness of digitalis[17-19] makes it the agent of choice, provided it is not implicated in the production of the arrhythmia. In our experiences, digitalis was highly successful in both normal and diseased hearts.

Although quinidine and procaine amide[20-22] are moderately effective, their incidence of success is less than that of digitalis. Their cardiac depressing action

and occasional lowering of the blood pressure are undesirable. Vasopressor agents are indicated if the blood pressure has fallen to shock levels.

Prevention of recurrences frequently resolves itself into determining the precipitating factors and abolishing them.

SUMMARY

1. An analysis is presented of 175 consecutive patients with supraventricular paroxysmal tachycardia seen in a teaching hospital practice over a period of 15 years.

2. Underlying organic heart disease was found in 131 patients (75 per cent), all of whom represented, in general, an older age group than the patients with normal hearts. Arteriosclerosis and hypertension were the most frequent etiologies, being found in 88 (67 per cent) of the cases with diseased hearts.

3. Of the supraventricular tachycardias in patients with organic heart disease, 45 (35 per cent) were complicated by second and third degree atrioventricular block, which usually could be attributed to complicating digitalis intoxication.

4. Serious clinical symptoms were only rarely observed in patients with normal hearts. In contrast, chest pain, heart failure, and shock were frequent manifestations of the disorder in organic heart disease.

5. Aberration of the QRS complexes during tachycardia was as frequent in normal hearts as in diseased hearts. Atrial rates were noted to be higher in the group with atrioventricular block, resulting in confusion of the electrocardiographic diagnosis with slow atrial flutter. The diagnostic criteria are outlined.

6. The usual methods of termination, utilizing carotid sinus pressure mechanical reflex increase in vagus tone, were much less effective in the patients with organic heart disease than in normal patients. If such measures failed, digitalis therapy was found to be the most effective method if it was not a factor in the production of the rhythm disorder.

7. Paroxysmal supraventricular tachycardia with atrioventricular block presents a special problem in therapy. There is usually gratifying restoration to sinus rhythm upon discontinuation of digitalis and administration of potassium salts.

8. The prognosis of these disorders depends upon the underlying etiology. In myocardial infarction it is uniformly poor, but a few cases can be salvaged by proper therapy.

9. Methods of management in other unusual situations, and prevention of recurrences are discussed.

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The Occurrence of a Rapid Ventricular Rate During Atrial Fibrillation as a Paradoxical Manifestation of Digitalis Intoxication

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INTRODUCTION

There is probably no clearer indication for the use of digitalis than in congestive heart failure associated with atrial fibrillation and a rapid ventricular response. The action of digitalis in blocking many of the atrial impulses at the A-V node, as well as directly reducing ventricular excitability, slows the rate of the ventricles.[1] Because the ventricular rate usually reflects the adequacy of digitalization in this situation, it has long served as a valuable guide to the dosage.[2]

Although it is well known that during atrial fibrillation digitalis overdosage may excessively decrease ventricular rate,[3] it is not generally recognized that digitalis intoxication may occasionally be manifest by a marked increase in ventricular response to the fibrillating atria.

The purpose of this paper is to present 3 patients with long-standing atrial fibrillation and advanced heart failure who had marked increases in ventricular rate while taking large doses of digitalis. The increase in ventricular rate in these patients seemed to be related to digitalis toxicity, precipitated by mercurial diuresis.

CASE REPORTS

CASE 1.—F. P. was a 72-year-old woman with a 4-year history of congestive heart failure. She had been taking 0.1 Gm. of digitalis leaf daily for 4 years and had occasionally required mercurial diuretics. Her appetite had been poor for the previous 6 months. Two months prior to admission she had become progressively more dyspneic and had noted pretibial edema. She had become weaker and 2 weeks prior to admission had noted abdominal swelling. During this period she had transitory episodes of palpitation of the heart. Anorexia, nausea, and vomiting had been prominent during the week preceding admission.

She appeared chronically ill. The temperature was 98.6° F., respirations 32 breaths per minute, blood pressure 120/60 mm. Hg, and the pulse was irregular at 100/min. The patient was moderately thin and showed signs of recent loss in weight. Breathing was labored. The neck veins were distended. There were signs of fluid in the right pleural cavity and congestion

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of both lungs. The heart was enlarged. The first sound was obscured by a harsh Grade 3 systolic murmur at the apex. The abdomen was moderately distended, and a fluid wave was present. The liver was enlarged, and both lower extremities were markedly edematous.

Urinalysis, hemoglobin, hematocrit, white blood count and differential were normal. The serum on admission showed: CO_2 combining power, 29 mM./L.; chloride, 102 mEq./L.; sodium, 136 mEq./L.; potassium, 3.2 mEq./L. A chest x-ray showed marked cardiac enlargement, fluid in the right pleural cavity, and evidence of pulmonary congestion. An electrocardiogram on admission showed atrial fibrillation with a ventricular rate of 130/min., and frequent multifocal ventricular premature contractions.

Because of gastrointestinal symptoms and multifocal ventricular extrasystoles, digitalis was discontinued. She was given mercurial diuretics on several occasions. The patient lost 12 pounds during her first week in the hospital. At the end of the second week, despite some improvement in her clinical condition, the ventricular rate continued to be rapid. For this reason she was given 2.75 mg. of digoxin in divided doses, and then maintained on digitalis leaf, 0.1 Gm. daily. Despite this treatment, the ventricular rate failed to slow and continued at about 130/min.

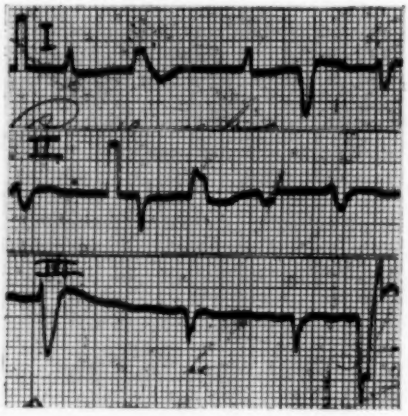

Fig. 1.—(Case 1.—F. P.) Atrial fibrillation with ventricular rate of about 110/min. Multifocal ventricular extrasystoles suggest digitalis toxicity. This record was taken 3 days prior to onset of the rapid ventricular rate shown in Fig. 2,*A*.

Twice during her third week in the hospital she was given mercurial diuretics intramuscularly. Following this she lost 6 pounds. Anorexia continued, and intake of food and fluid remained poor. An electrocardiogram on the eighteenth hospital day (Fig. 1) showed atrial fibrillation with a ventricular rate of 110/min., and numerous multifocal ventricular extrasystoles. Despite this evidence of digitalis toxicity, digitalis was continued for the next 3 days, and on the twenty-first hospital day she was given 2 c.c. of Thiomerin intramuscularly. Later that evening the patient suddenly developed severe pulmonary edema. Serum drawn that morning (prior to the mercurial diuresis) showed a CO_2 combining power of 31 mM./L.; chloride, 97 mEq./L.; sodium, 120 mEq./L.; and potassium, 3.0 mEq./L. An electrocardiogram at this time showed atrial fibrillation with a ventricular rate of about 200/min. (Fig. 2,*A*). Bedside chest x-ray was consistent with acute pulmonary edema. She was treated with bloodless phlebotomy, oxygen by mask, and was given an intravenous solution containing 20 mEq. of potassium as potassium chloride in 250 c.c. of 5 per cent dextrose in water. One-half hour later, after receiving approximately 10 mEq. of potassium, the ventricular rate had decreased to about 150/min. (Fig. 2,*B*). At this time she was given 0.5 mg. of digoxin intravenously, in the belief that additional digitalis was required to slow the ventricular rate. Two hours after the intravenous digoxin had been given, the rate had again increased to about 180/min., and the QRS duration had increased from 0.07 to 0.12 second (Fig. 2,*C*). Although she had already received 20 mEq. of potassium, another 40 mEq. of potassium in 400 c.c. of 5 per cent dextrose in water was infused at the rate of 0.25 mEq. per minute. One-half hour after the second infusion had been started, the intraventricular block had disappeared,

and the ventricular rate had decreased to 150/min. (Fig. 2,*D*). One and one-half hours after the second infusion had been started, the ventricular rate had decreased to about 85/min., and the patient was clinically improved (Fig. 2,*F*). By early morning the pulmonary edema had cleared, and she was sleeping restfully. An electrocardiogram at this time showed atrial fibrillation with a ventricular rate of about 80/min. No ventricular premature beats were noted.

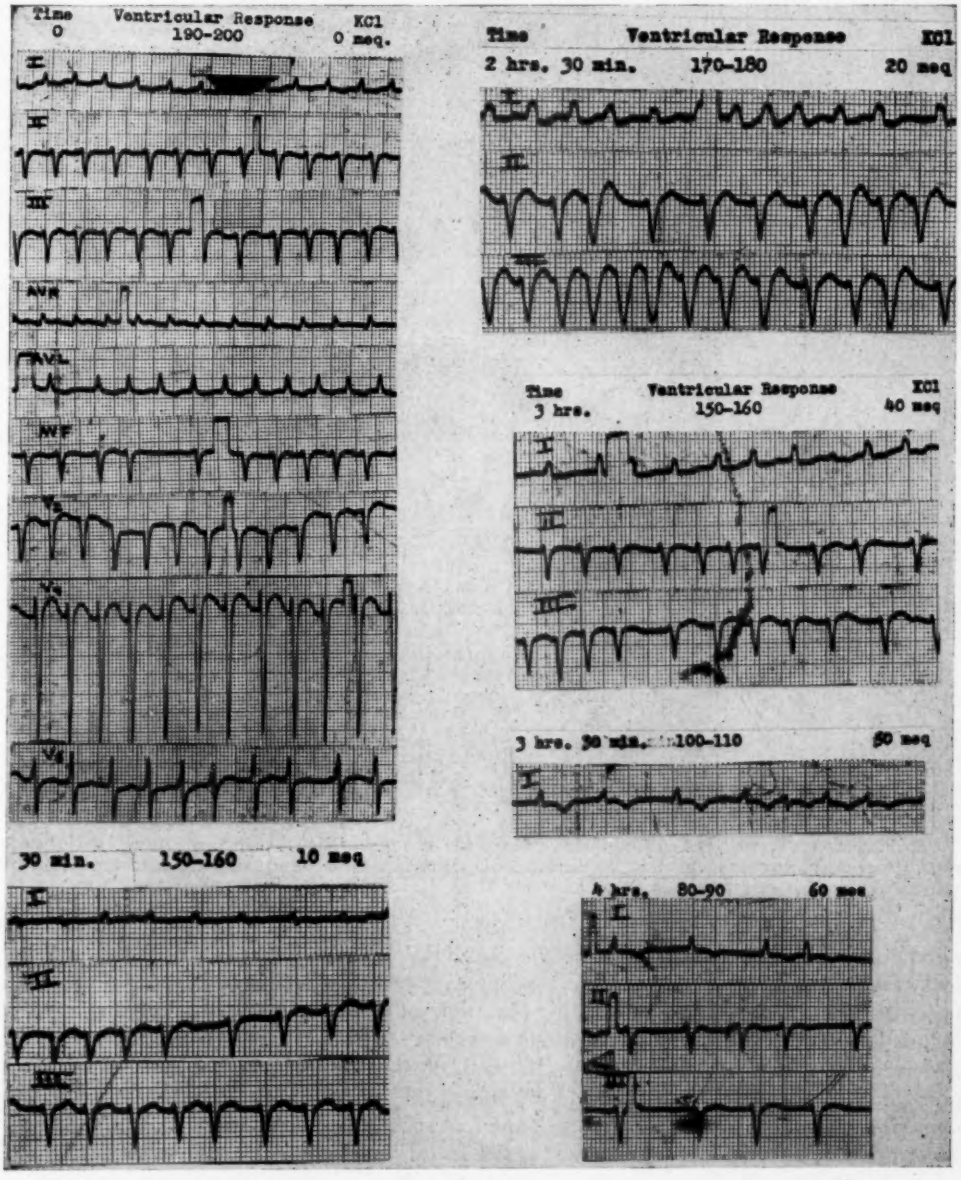

Fig. 2.—(Case 1.—F. P.) Despite the evidence of digitalis toxicity seen in Fig. 1, the patient was continued on digitalis and mercurials. *A*, Three days later the patient developed acute pulmonary edema. ECG shows atrial fibrillation with a ventricular rate of 200/min. *B*, Thirty minutes later, after 10 mEq. of potassium had been given I. V., the rate had decreased to about 155/min. At this time 0.5 mg. of digoxin was given I. V. *C*, Two hours after digoxin. Rate had increased to 180/min., and intraventricular block appeared. A second infusion of potassium was started immediately. *D*, Thirty minutes later the rate decreased to 150/min., and the intraventricular block was gone. *E*, and *F*, Progressive decrease in ventricular rate to 100/min. and finally to 85/min. at the end of the infusion of potassium.

CASE 2.—E. R. was a 24-year-old woman with a history of rheumatic fever at the age of 5 years. Signs of mitral stenosis and insufficiency and tricuspid insufficiency had been noted during past admissions. Atrial fibrillation had been present for the past 12 years.

During the past 2 years her activities had been severely limited by dyspnea and weakness on moderate exertion. Digitalis, periodic mercurials, and a low-salt diet had been necessary to control ascites and swelling of her lower extremities. During the 3 months prior to admission

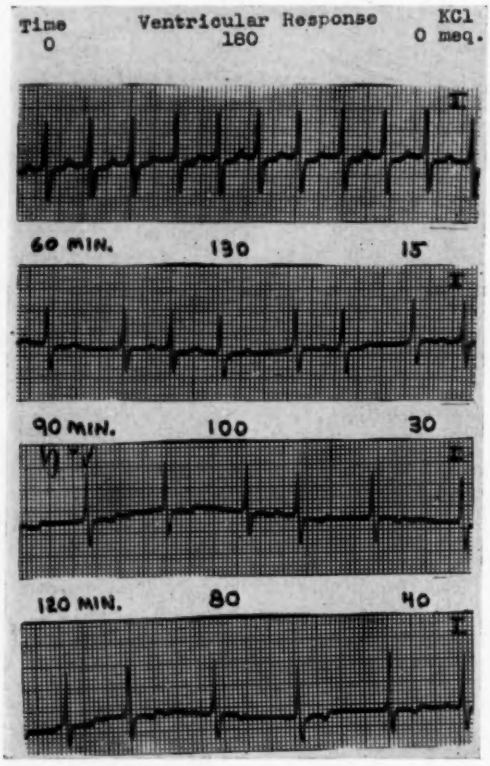

Fig. 3.—(Case 2.—E. R.) Atrial fibrillation with a ventricular rate of 180/min. Serial records show a progressive decrease in ventricular response over a 2-hour period during infusion of 40 mEq. of potassium.

she had been taking 0.3 Gm. of digitalis leaf daily, and she received mercurial diuretics by injection twice weekly. Despite this aggressive treatment, abdominal swelling, dependent edema, and dyspnea had been increasing. The patient had reduced digitalis to 0.1 Gm. daily one week prior to admission because she had begun to feel weaker than usual, anorectic, and nauseated. On the morning of admission she had taken 0.2 Gm. of digitalis leaf and had been given 2 c.c. of Thiomerin intramuscularly. In the late afternoon, following diuresis from the morning dose of Thiomerin, she had become extremely weak and had noted the sudden onset of distressing palpitations of the heart.

The patient was thin and appeared acutely ill. There were marked tachypnea, orthopnea, and sweating. The temperature was 100.8° F., apical pulse 180/min., radial pulse 80/min.; respirations were 42 breaths per minute, and blood pressure was 110/70 mm. Hg. The neck veins were distended in the upright position. Except for the signs of fluid at the right base, the lungs were clear. The heart was enlarged. The point of maximal impulse was felt in the sixth intercostal space at the midaxillary line. Systolic and diastolic apical thrills were palpated. A Grade 3 rumbling diastolic murmur, terminating in a loud first sound, followed by a Grade 3 harsh systolic murmur, was heard at the apex. The abdomen was protuberant; shifting dullness

and a fluid wave were present. The liver was enlarged and tender. Marked dependent edema of the lower extremities, extending to the knees, was present.

Urine examination was normal. Hemoglobin, white blood count, differential and sedimentation rates were unremarkable. Total bilirubin was 1.6 mg. per cent, and blood urea nitrogen was 19 mg. per cent.

The electrocardiogram (Fig. 3, top) showed atrial fibrillation with a ventricular response of 180/min. Since additional digitalis did not seem to be indicated, an intravenous solution containing 40 mEq. of potassium as potassium chloride in 500 c.c. of 5 per cent dextrose in water was administered at a rate of about 0.25 mEq. per minute. Serial electrocardiograms showed progressive slowing over the 2-hour period of treatment (Fig. 3). Two hours after treatment had been initiated and 40 mEq. of potassium had been administered, the ventricular rate had decreased to about 80/min., and the patient had obtained marked clinical and subjective improvement.

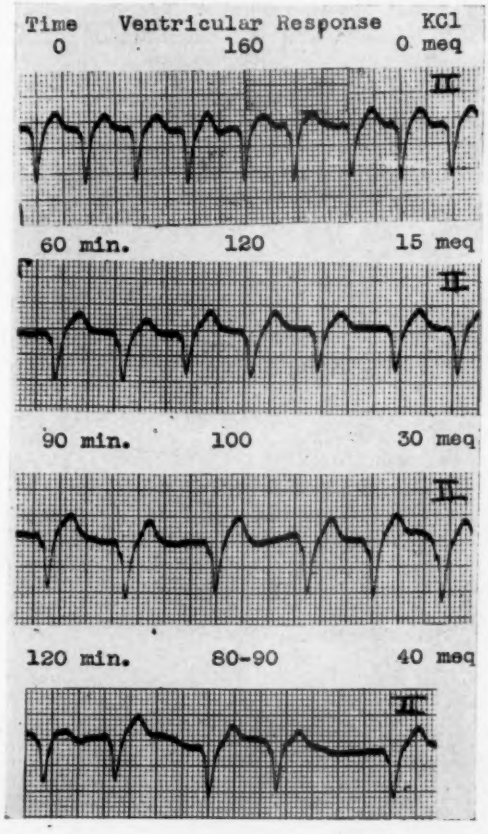

Fig. 4.—(Case 3.—J. W.) Atrial fibrillation and left bundle branch block. Serial records show progressive slowing of the ventricular rate over a 2-hour period during which 40 mEq. of potassium was infused.

CASE 3.—J. W. was a 56-year-old Negro with a 5-year history of arteriosclerotic heart disease. The patient had been receiving digoxin, 0.5 mg. daily, for the past 4 years following a myocardial infarction. Atrial fibrillation had been present for several years. Eight months prior to admission he had noted increasing dyspnea on exertion and had begun to receive ammonium chloride and mercurial diuretics periodically. During the 6 months preceding admission, the patient had required mercurial diuretics twice a week to control his congestive failure. Two weeks prior to admission his dyspnea had become more marked, and dependent edema extending above the knees had been noted. Three days before admission he had noted squeezing substernal pain radiating

to the shoulders and back. Dyspnea had become marked, even at rest. He had received Thiomerin one day prior to admission.

The patient was a well-developed man who was markedly tachypneic and disoriented. The nail beds were cyanotic. The blood pressure was 80/0 mm. Hg, respirations 40 breaths per minute, temperature 99° F., apical pulse 160/min., radial pulse between 80 and 100/min. and irregular. The skin was cold and moist. Despite the tachypnea, the lungs were clear. Neck veins were distended and pulsating in the sitting position. The heart was markedly enlarged to the left. A systolic apical thrill was palpable. P_2 was greater than A_2. There was a Grade 4 systolic murmur heard at the apex and radiating over the precordium generally. The abdomen was soft, and the liver was enlarged and tender. The extremities were edematous to the knees.

A bedside chest x-ray showed generalized cardiac enlargement, but the lung fields were relatively clear. The electrocardiogram (Fig. 4, top) showed atrial fibrillation with a ventricular response of 160/min. and a left bundle branch block.

Long-term maintenance on digoxin and biweekly mercurial injections prompted us to give him a trial of intravenous potassium before administering further digitalis. He was given an intravenous infusion of 40 mEq. of potassium as potassium chloride in 500 c.c. of dextrose and water in 2 hours at a rate of 0.25 mEq. per minute. Serial tracings (Fig. 4) showed a progressive decrease in ventricular rate during the 2-hour period of infusion. The ventricular rate, initially 160/min., slowed progressively over a 2-hour period to 80/min. Serum electrolytes obtained 4 hours after the potassium had been infused were: chloride, 85 mEq./L.; CO_2 combining power, 18.6 mM./L.; potassium, 6.1 mEq./L.

As his ventricular rate decreased, his clinical state improved. The blood pressure rose to 110/70 mm. Hg from the initial shock level, and the loud murmur disappeared. His ventricular rate varied between 80 and 100/min. over the next 12 hours. Urine output was scant, which precluded further potassium therapy. His blood pressure began to drop, and the ventricular rate began to increase 12 hours after his initial treatment. It became necessary to administer intravenous vasopressors to maintain his blood pressure. Eighteen hours after admission his blood pressure had again dropped to a shock level despite use of large amounts of norepinephrine. At this time ventricular tachycardia developed, which was converted to a sinus tachycardia with 0.6 Gm. of quinidine given intravenously. The sinus tachycardia was briefly sustained, however, and several hours later the rhythm reverted to ventricular tachycardia. This rhythm was followed by ventricular fibrillation, and death 23 hours after admission. Post-mortem examination revealed cardiomegaly (740 grams) with hypertrophy and dilatation of all chambers. There was evidence of an old myocardial infarction. Mural thrombi were present in the left ventricle, right and left atria. Old and recent infarctions of the lung were present. There was chronic passive congestion, fibrosis, and patchy necrosis of the liver. Multiple old healed infarcts of both kidneys were found.

DISCUSSION

When a marked increase in the ventricular rate occurs in the course of patients with atrial fibrillation being treated with digitalis, several cardiac mechanisms must be considered. These are: (1) ventricular tachycardia, (2) nodal tachycardia, or (3) an increase in ventricular response to the atrial fibrillation.

In order to clarify the mechanism involved in the rapid ventricular rate in our patients, the pretreatment electrocardiograms were carefully studied. Definite beat-to-beat irregularity of the R-R intervals was observed. This irregularity became progressively more obvious as the ventricular rate slowed during the administration of potassium (Figs. 2-4). In addition, the form and duration of the QRS complexes remained unchanged during the administration of potassium and when comparison was made with older records. It was concluded from these facts that the tachycardia represented an increase in ventricular response to the atrial fibrillation rather than an alteration in the pacemaker mechanism.

Because these patients had all become gravely ill during the tachycardia, slowing the ventricular response had become an urgent objective of treatment. Although atrial fibrillation with rapid ventricular response associated with refractory heart failure might well have been regarded as a classical indication for rapidly and aggressively increasing the dose of digitalis, there were a number of very good reasons for suspecting that these patients might have been suffering already from digitalis intoxication.

Each of the patients had exhibited a strikingly similar clinical pattern of evolution prior to the onset of the rapid ventricular rate. In each patient, atrial fibrillation and cardiac failure had been present for several years. During the months preceding admission, increasing heart failure and clinical deterioration had been occurring despite treatment with increasing doses of digitalis, frequent mercurial diuretics, and rigid salt restriction.

In each case a recently administered mercurial diuretic followed by effective diuresis seemed to trigger the marked increase in ventricular rate. Lown and Levine[4] have shown that potassium diuresis following the administration of a mercurial diuretic often precipitates digitalis toxicity. It has been demonstrated that excessive potassium diuresis occurs when patients with long-standing congestive failure and edema are given mercurial diuretics, particularly when rigid salt restriction has been effected.[5] Lown and Levine[4] have defined the post-mercurial redigitalization phenomenon as "a state of increased myocardial sensitivity to the toxic properties of digitalis resulting from a negative potassium balance precipitated by diuretic therapy."

The evidence for digitalis toxicity in Case 1, the first case observed, was particularly striking. This patient entered the hospital with classical symptoms, signs, and electrocardiographic evidence of digitalis toxicity (Fig. 1). Despite this, she had received large doses of digitalis and frequent mercurial diuretics without a decrease of the ventricular rate or improvement of her heart failure. Although the electrocardiogram had shown frequent multifocal premature ventricular beats, thought to represent evidence of digitalis toxicity, 3 days prior to the paroxysmal increase in ventricular rate (Fig. 1), digitalis had been persistently continued. Because the serum potassium level had already been low, it was felt that the diuresis which preceded the paroxysmal increase in ventricular response would have further depleted potassium, and that this loss may have been related to the tachycardia. For this reason and also because of the therapeutic value of the administration of potassium in digitalis toxicity,[4,6-8] it was decided to give intravenous potassium to this patient.

The administration of potassium in each of these patients resulted in a prompt and progressive decrease in the ventricular rate (Figs. 2-4). When the infusion of potassium had been interrupted and digoxin given (Case 1), not only had there been an increase in the ventricular response, but intraventricular block had been provoked (Fig. 2,*C*). However, the administration of additional potassium again slowed the ventricular rate and eliminated the intraventricular block in this patient (Fig. 2,*D* and *F*). These observations strongly suggested that the rapid ventricular response which occurred during the course of management of

these patients with long-standing atrial fibrillation may have appeared as a paradoxical manifestation of digitalis intoxication in the presence of, or precipitated by, depletion of potassium.

The interaction of digitalis and potassium on the heart is profound. Digitalis in toxic concentration produces disturbances in the permeability of the myocardial fiber to both potassium and sodium.[9] Critical electrolyte shifts not only potentiate digitalis toxicity, but the toxic effects persist throughout the duration of electrolyte derangement.[10] There is strong evidence that digitalis toxicity is associated with the depletion of myocardial potassium in general, and that the loss is selectively marked in those chambers that are failing.[11-13] In both experimental animals and man, depletion of potassium potentiates the toxic effects of digitalis on the heart.[4,6,14] Conversely, the administration of potassium reverses and suppresses the cardiotoxic manifestations of overdosage.[4,6-8]

Three additional cases of atrial fibrillation with a rapid ventricular response were observed during the period of this study. These patients had not been in advanced congestive failure, and, although they had been taking digitalis, none had received mercurial diuretics. They had each been given a trial of 60 mEq. of potassium intravenously, without appreciable slowing of the ventricular rate. In these patients the ventricular rate was decreased by increasing digitalis dosage. This suggested that a comparable dose of potassium did not in itself cause ventricular slowing during atrial fibrillation unless digitalis toxicity or depletion of potassium were also present.

Because atrial fibrillation with a rapid ventricular rate is so generally regarded as an indication of underdigitalization, it would probably be unrecognized as evidence of digitalis toxicity. In a recent report of 100 cases of digitalis intoxication, 10 were considered to have had atrial fibrillation with a rapid ventricular rate.[15]

Lown and Levine[4] have stressed the emergence of a rapid "regular" ventricular rate during atrial fibrillation as evidence of digitalis toxicity. The regularity of the ventricular rate which they have stressed and the examples which they have presented imply that nodal or ventricular tachycardia or paroxysmal atrial tachycardia with block had been present in their cases.

This report seeks to draw attention to a generally unrecognized toxic potential of the cardiac glycosides during atrial fibrillation which may be manifest purely by an increase in the ventricular response to the fibrillating atria without emergence of a different pacemaker. Since this paradoxical effect of digitalis poisoning in producing a rapid ventricular response during atrial fibrillation seems prone to occur in patients with advanced congestive failure after aggressive therapeutic measures have already been exhausted, it may be mistakenly identified as an end state of cardiac decompensation rather than a remediable complication of therapy. Furthermore, since the occurrence of this paradox represents advanced digitalis toxicity and simulates a situation in which digitalis is indicated, the risk of fatal overdosage is acute. In doubtful cases, it is probably safer to give a trial dose of potassium before giving additional digitalis, even if the serum potassium concentration is normal, since severe depletion of total body potassium may be present without a lowering of the serum potassium concentration.[6,17]

A number of experimental observations provide a possible theoretical explanation for the paradoxical increase in ventricular rate during atrial fibrillation when digitalis overdosage is associated with potassium depletion. It has been shown that a large dose of digitalis injected directly into the A-V node may cause a decrease in nodal delay.[18] Digitalis frequently increases the rate of fibrillating atria.[19] When the serum potassium concentration is diminished, there is a decrease in the resting membrane potential toward the critical threshold potential, which enhances the excitability of cardiac tissue.[20a] It is well known that the failing, partially anoxic myocardium is hyperexcitable and responds to stimuli ordinarily incapable of eliciting contraction.[2]

From these data it is possible to postulate a theoretical basis for a paradoxical increase in ventricular response during atrial fibrillation when overdosage of digitalis and depletion of potassium coexist. This might result from the combined effect of decreased block at the A-V node facilitating the transmission of more rapidly formed atrial impulses to a hyperexcitable ventricular musculature.

The therapeutic effects of potassium on the rapid ventricular rate may be explained by the effect of this cation on several electrical properties of the heart. An elevated concentration of serum potassium results in a marked decrease in the velocity of impulse propagation.[21] Elevating the concentration of serum potassium depresses cardiac excitability, and the A-V node is particularly sensitive to increments in concentration of serum potassium.[20b] Hoff[22] has demonstrated that in both man and dog, A-V conduction disappears at a concentration of serum potassium of 8 or 9 mEq. A-V block of varying degree is a characteristic electrocardiographic finding in potassium intoxication.[20] Potassium may therefore exert its therapeutic effect on the rapid ventricular rate by decreasing the velocity of impulse conduction through the A-V node, restoring resting membrane potential to normal, and suppressing the excitability of the ventricles.

The cases presented were collected in less than one year. It seems probable, therefore, that this paradoxical effect of digitalis on ventricular response is not rare.

SUMMARY

1. Three patients with long-standing atrial fibrillation were observed to have an increase in ventricular response to atrial fibrillation while taking large doses of digitalis.

2. The increase in rate in each instance followed recent administration of a mercurial diuretic and was thought to be associated with loss of potassium during diuresis.

3. Administration of intravenous potassium resulted in prompt and progressive slowing of the ventricular rate over a 2-hour period.

4. In one case, digoxin given intravenously, after the rate had been slowed with potassium, caused the rate to increase. Additional potassium again effected slowing.

5. The evidence suggests that during atrial fibrillation, digitalis toxicity may be paradoxically manifest by an increase in ventricular response without alteration of the pacemaker mechanism.

6. Since this paradoxical response simulates a classical indication for digitalis, it represents a dangerous paradox if unrecognized as a toxic potential of the cardiac glycosides.

7. This manifestation of toxicity seems prone to occur in patients with refractory congestive failure treated with rigid salt restriction, frequent mercurial diuretics, and large doses of digitalis.

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Chaotic Heart Due to Metastatic Synovioma

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A case of synovioma metastatic to the heart is reported because of the multiplicity of arrhythmias produced by the tumor and the lack of metastases other than in the myocardium.

CASE REPORT

A 22-year-old Negro was admitted to Letterman Army Hospital in September, 1957. The patient had noted recurrent episodes of palpitation with accompanying lightheadedness for 4 weeks prior to admission to hospital. These episodes of palpitation were abrupt in onset, brief in duration, and unpredictable in their occurrence. Attacks of tachycardia occurring during the last 2 weeks prior to admission were accompanied by dyspnea, a feeling of substernal tightness, sweating, and anxiety. Four attacks of tachycardia resulted in brief syncope without convulsions but with urinary incontinence. Upon initial examination in the outpatient clinic, an irregular pulse was noted. An electrocardiogram revealed brief bursts of ventricular tachycardia. Examination during the recording of the electrocardiogram revealed no palpable pulse and no audible heart sounds during bursts of tachycardia (Fig. 1,*A*). The patient was admitted to the hospital. The past history was significant in that a left supracondylar amputation for synovial sarcoma of the calf had been performed at Brooke Army Hospital in October, 1956.

Physical examination revealed a muscular young man with a well-healed left mid-thigh amputation stump. There were no masses or other abnoramalities in the stump. The blood pressure was 140/60 mm. Hg. The pulse was 120 per minute, with brief periods, occurring at irregular intervals, during which the pulse was not palpable and heart sounds were not audible. Physical examination was otherwise normal.

The following laboratory data were either normal or negative: urinalysis, serologic test for syphilis, leukocyte count and differential, hematocrit and erythrocyte sedimentation rate. Radiologic studies of the chest and skull were normal. A ballistocardiogram was abnormal. An electrocardiogram taken on admission revealed bursts of ventricular tachycardia but was otherwise normal.

Upon admission to the hospital, the patient was treated with procaine amide, 1.0 Gm. administered slowly intravenously with continuous electrocardiographic monitoring. This therapy resulted in the disappearance of the episodes of ventricular tachycardia. The patient, asymptomatic and with a normal electrocardiogram, was discharged to the outpatient clinic on an oral maintenance dose of quinidine sulfate, 0.6 Gm. every 6 hours. On reporting back for outpatient follow-up, he stated he had had no further syncope, but that he had noted occasional brief episodes of palpitation and lightheadedness.

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On Oct. 8, 1957, he was readmitted to the hospital without any change in symptoms, because of the appearance of first and second degree atrioventricular block which was thought to represent quinidine toxicity (Fig. 1,*B*). There was no other electrocardiographic evidence of quinidine toxicity. Twenty-four hours after stopping quinidine sulfate there were multifocal ventricular beats, atrial flutter with 2:1 to 5:1 response, first and second degree atrioventricular block, and

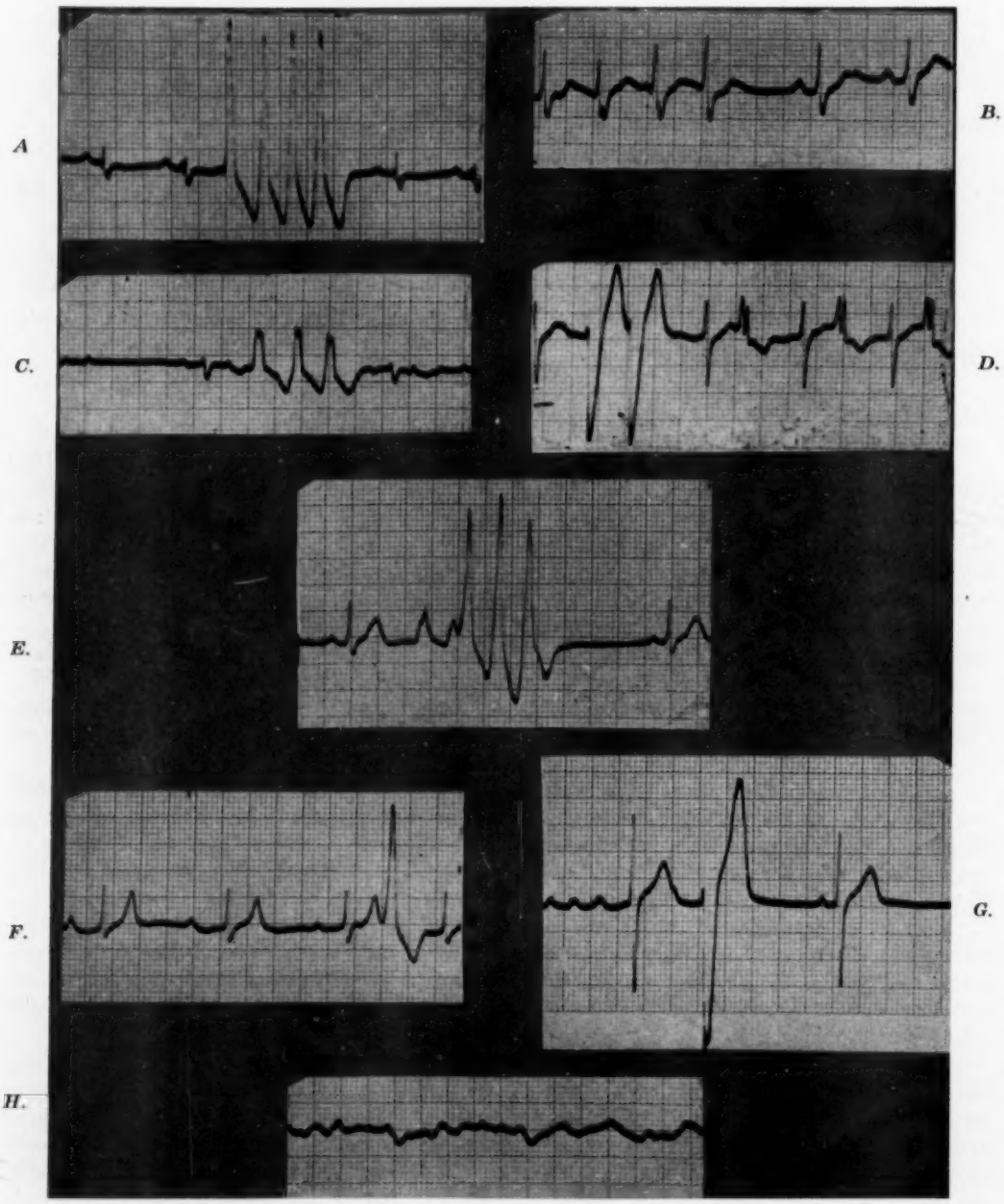

Fig. 1.—*A*, Initial ECG. *B*, ECG on readmission on quinidine therapy. *C* and *D*, Tracings recorded after discontinuance of quinidine, showing atrial flutter, second degree heart block, and multifocal ventricular beats. *E*, ECG at start of infusion of potassium chloride. *F*, Tracing made after 8.5 mg. of potassium chloride intravenously, with first degree A-V block and only rare unifocal ventricular beats. *G*, ECG six hours before death. *H*, Terminal ECG.

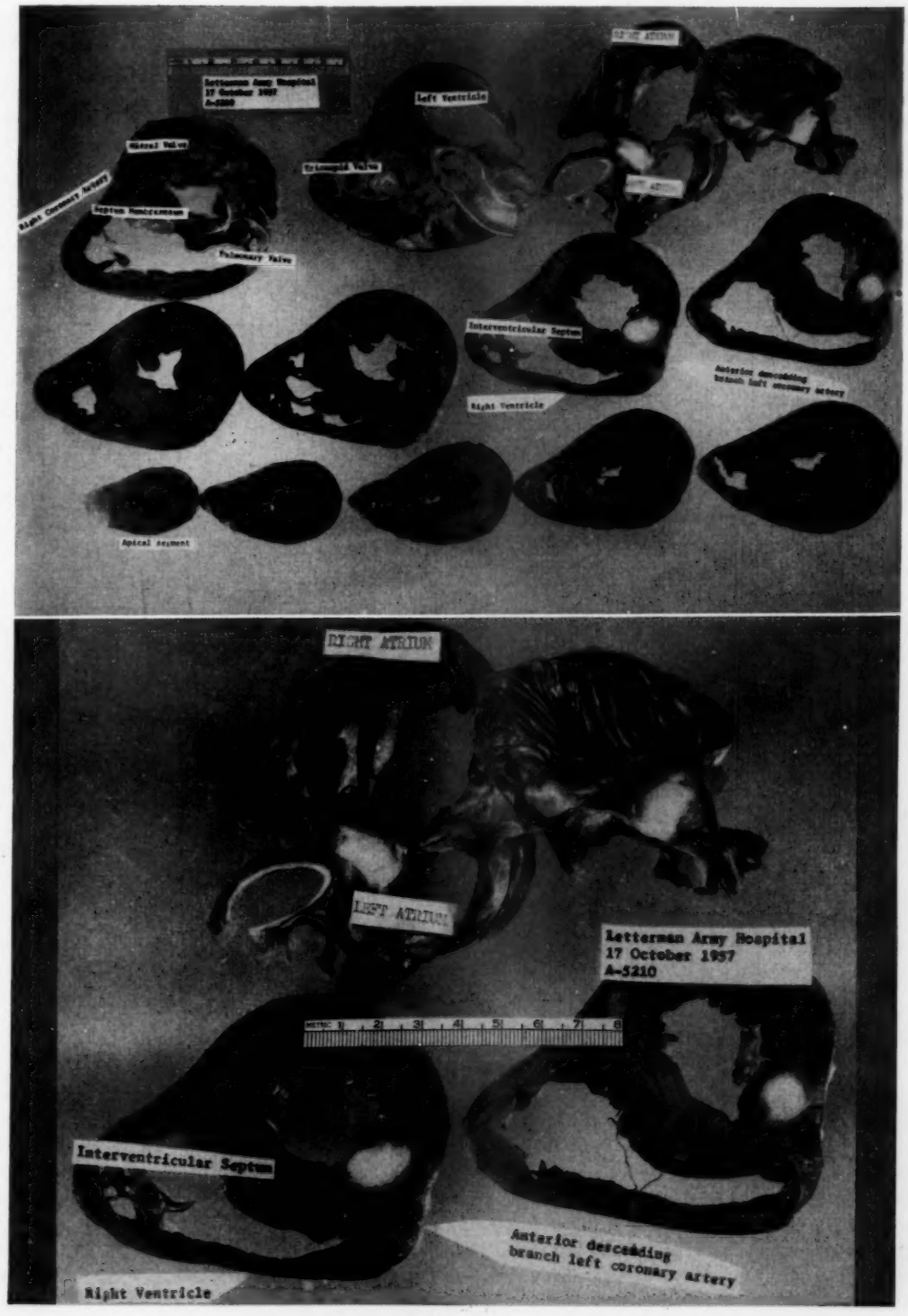

Fig. 2.—Tumor foci in left ventricle and interatrial septum. (U. S. Army photograph.)

sinus rhythm, all occurring in rapid and chaotic sequence (Fig. 1,*C* and *D*). Despite these findings in the electrocardiogram, the patient complained only of a slight increase in his palpitations. Quinidine was not given because of the atrioventricular block. A trial dose of 7.5 mg. of isoproterenol sublingually, in the hope of abolishing the atrioventricular block and stimulating the sinoauricular node, had no immediate effect. One hour after the administration of the trial dose of isoproterenol, a 5- to 10-minute period of supraventricular tachycardia, with a rate of 180 per minute, was noted. The following day, rapid intravenous infusion of 8.5 mEq. of potassium chloride abolished for 5 minutes all arrhythmias except the Wenckebach phenomenon (Fig. 1,*F*), but the former chaotic rhythm recurred (Fig. 1,*E* and *G*). On Oct. 12, 1957, the patient died following three short generalized convulsions. A terminal electrocardiogram revealed ventricular fibrillation (Fig. 1,*H*).

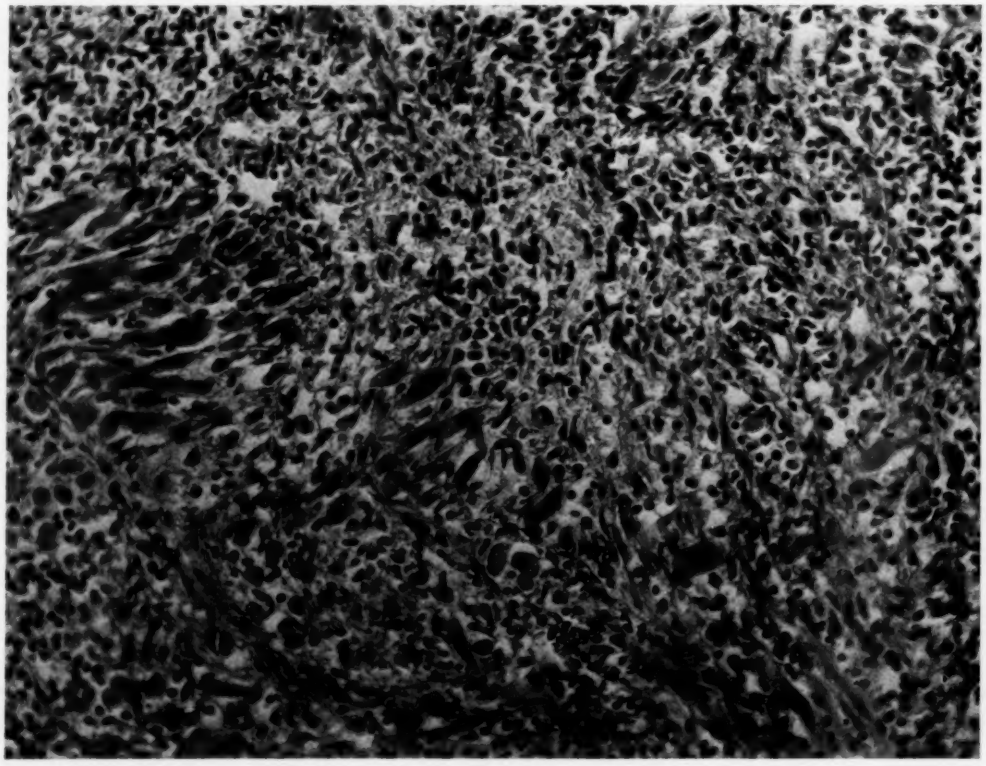

Fig. 3.—Microscopic appearance of the tumor. (U. S. Army photograph.)

Postmortem examination revealed no evidence of tumor in the amputation stump. Abnormal pathologic findings were limited to the heart. The heart weight and external appearance were normal. On section, the heart contained two areas of firm, white tumor (Fig. 2). The larger of these tumors measured 2.0 cm. transversely, 1.5 cm. anteroposteriorly, and 3.0 cm. longitudinally. This tumor lay in the interatrial septum in a longitudinal plane overriding the septum membranosum of the interventricular septum and creating a bulge into the right atrial cavity in the approximate position ascribed to the bundle of His. The second metastasis was entirely within the anterior wall of the left ventricle at its junction with the interventricular septum, 1 cm. below the annulus of the aortic valve and extending 4 cm. apically. It measured 1.5 by 1.1 cm. in the transverse and anteroposterior planes. The microscopic appearance of both areas was similar, consisting of an intertwining, irregular, densely packed, fasciculated pattern. The typical cell resulted in a small fibroblast with irregular oval nuclei and eosinophilic stellate cytoplasm (Fig. 3). There were no other metastases.

DISCUSSION

Synoviomata are highly malignant tumors arising in the lower extremity in 80 per cent of the cases, usually near the knee. They are usually outside but near bursae and tendon sheaths.[1] In 104 cases reported by Haagensen,[1] only 3 survived 5 years and none had cardiac metastasis. Eight of 23 cases followed from 16 to 54 months postoperatively were well in the series reported by Bennett.[2] Carling,[3] however, reported a 40 per cent 5-year survival rate.

The tumor is usually painful and, therefore, is operated upon and diagnosed promptly in the majority of cases. However, a few tumors are painless, and in 1 case one was present for as long as 16 years before diagnosis.[1] The diagnosis should always be considered when "chocolate" material is found in any cyst near a bursa.[4] The treatment of choice is high amputation, or if this cannot be done, as wide an excision as possible. Attempts at local excision are almost uniformly unsuccessful, and biopsy for diagnosis should be carried out with a view to definitive surgery as soon as the diagnosis can be pathologically confirmed.[1,4] Synoviomata are quite radioresistant, and Haagensen[1] states that no 5-year survivals or significant palliative value resulted from radiation therapy.

The incidence of malignant metastatic involvement of the myocardium varies from 3.4 to 20 per cent of all malignancies.[5-7] Leukemia and lymphoma may involve the heart in as high an incidence as 24 and 44 per cent, respectively.[8] In 146 cases of metastasis to the myocardium reported by Pritchard,[5] only 1 had no other metastatic focus. Gassman[9] reported 217 cases with myocardial and/or pericardial involvement, of which 18 had no other metastasis. Earlier literature[10] indicated a preponderance of right-sided cardiac involvement, but DeLoach[7] found no appreciable difference in his cases.

In reports of cardiac metastases, autopsy findings correlate fairly well with abnormal clinical and electrocardiographic findings, but the majority are clinically "silent." Accurate ante-mortem diagnosis of cardiac metastasis is more difficult, as evidenced by a total of only 40 cases so diagnosed by 1955.[9] Congestive failure has followed pericardial implants associated with effusion. Vena caval involvement has been reported.[7,11] On the other hand, surprisingly large amounts of myocardium may be replaced by tumor without congestive failure.[12] As might be expected, valvular implants are rare. Congestive failure due to arrhythmias is relatively common.

Electrocardiographic changes are nonspecific and include abnormal Q waves, transient or long-term ST-T wave abnormalities, flat or inverted T waves, and any type of arrhythmia or conduction defect.[7-22] There is good retrospective correlation between autopsy findings of right atrial involvement and atrial arrhythmias and A-V node involvement and A-V block.[11,14,17,20] Any arrhythmia or conduction defect in a patient with malignancy and without evidence of other heart disease should arouse strong suspicion, if not diagnosis, of myocardial implants or invasion. Electrocardiographic findings other than arrhythmias and conduction defects are too nonspecific to be of aid in the diagnosis of metastasis to the myocardium. Pericardial effusion occurring in a patient with a history

of malignancy strongly suggests pericardial involvement with metastases. Except for those cases with pericardial effusion, changes in cardiac contour secondary to tumor are exceedingly rare.[6-8,21]

There have been no reported cases of cure of myocardial metastasis. Palliative x-ray to the precordium has been recommended, but rarely reported. In one case, 2 months of symptomatic relief followed rather light precordial irradiation in a case with pericardial involvement with myeloblastoma.[18] The use of precordial radiation is contraindicated in cases in which the primary tumor is known to be resistant to radiation. Surgical removal of myocardial metastases has not been reported to date.

SUMMARY

The findings in a patient with synovial sarcoma metastasis to the myocardium are presented. Cardiac symptoms arose 11 months after diagnosis and amputation of the primary site. Chaotic rhythms and conduction defects characterized this case. At postmortem there were no metastatic foci except for those in the myocardium.

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Fetal Electrocardiography, With Special Reference to Early Pregnancy

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Notwithstanding positive demonstration of fetal electrocardiograms by Cremer,[1] Foa,[2] and others, as early as 1906, studies of fetal electrocardiography have not been given due attention by investigators. Inadequate instrumentation has played a part in this lack of development. Strassman[3] proposed a standardized technique, and Bell[4] was probably the first to record fetal electrocardiograms in a multiple pregnancy. More recent work by Southern[5] and by Bernstine and Borkowski[6] has shown improved technique and results, the latter workers having also provided a good review of the subject. In this report it will be shown that with new instrumentation and technique, fetal electrocardiography can be recorded in utero even early in pregnancy, and that application of bio-electric theory to the specific problems of fetal electrocardiography can be made.

METHOD AND MATERIALS

The equipment utilized for this investigation was one or more channels of a six-channel Offner Dynograph, employing the Model 9406 preamplifier. With this instrumentation, deflections of several centimeters for the fetal R wave are possible. In this system, RC coupling is used only in the preamplifier, the rest of the system being the direct-coupled chopper amplifiers of the Dynograph. In order to minimize base-line variation due to various slow signals (including the maternal T wave), a time constant of 0.04 second has been employed. One practical effect of this choice is to emphasize the fetal QRS complex. Paper speed has been routinely 25 mm. per second.

Two types of electrode arrangements have been used. In the first, German silver alloy disks 1 cm. in diameter were the electrodes, and these were placed in the desired positions after skin preparation. Electrode positions have included the following, depending partly upon the stage of the gestation: (1) midline bipolar leads, with the upper electrode just above the umbilicus and the lower electrode just above the symphysis pubis; (2) longitudinal bipolar leads on the right or left sides of the uterus, and transverse or horizontal bipolar leads placed suprapubically, especially in early pregnancy; (3) anteroposterior bipolar leads, with the anterior lead on the uterine fundus, and the posterior lead 10 cm. above the coccyx; (4) unipolar leads, in which an exploring electrode has been placed on the uterus, with a relatively indifferent electrode placed on the thigh.

The second type of electrode arrangement consisted of a series of special hand electrodes, which were silver buttons set in a plastic holder, with electrodes ordinarily spaced 10 cm. This hand electrode was of special importance in early pregnancy, and was applied with pressure so as to bring the electrodes closer to the fetal heart.

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Skin preparation consisted of applying ECG paste, rubbing the paste into the skin, and then carefully washing off the paste. The disk electrodes were then moistened with the paste, placed in position, and taped down with two strips of adhesive tape. For the hand electrodes, skin preparation was much the same; the paste was also applied to the electrodes and the assembly placed in position with moderate pressure.

A total of 260 fetal electrocardiograms from 145 patients has been recorded. In certain instances, as many as 16 consecutive recordings have been obtained from cooperative subjects, through the full gestational period.

Definitions.—The definition of terms employed is as follows: *f-ECG:* the fetal electrocardiogram in utero; *f-QRS:* the fetal QRS complex as observed with short time constants, as in this investigation, hence a somewhat more specific nomenclature; *newborn ECG:* the electrocardiogram of the newborn immediately after delivery, taken with the hand electrode on back or chest, or with standard Lead II; *electrical axis of the heart:* vector visualizing the resultant of all the differences of potential within the heart at the moment of the greatest deflection of the QRS complex.

RESULTS

Fig. 1 shows examples of the normal fetal electrocardiogram with the fetus presenting by the vertex. Since the objective of these investigations was to study the fetal ECG, electrode polarities were arranged so that in the normal vertex presentation of the fetus, the f-QRS would be upright. With this arrangement the maternal QRS was directed downward, i.e., in the opposite direction. The f-QRS was large and unmistakable. The faster rate of the fetal heart was demonstrated clearly, making identification of the fetal electrocardiogram easy.

In Fig. 2 are shown instances of relatively slow or fast maternal heart rates as well as examples of slowing and of acceleration of the fetal heart rate. The upper tracing shows an instance of a rapid maternal rate with a somewhat slowed fetal rate. In this instance the two rates were not markedly different, so that there was roughly one fetal complex to one maternal complex. The lower tracing shows the association of a slow maternal heart with a rapid fetal rate, so that there were often three fetal complexes to one maternal complex.

In Fig. 3 may be seen an interesting comparison of the fetal electrocardiogram in utero a few minutes before delivery, with the newborn electrocardiogram just after delivery. In this instance every effort was made to place the hand electrode on the newborn in the same relation to the fetal heart as was the case for the surface electrodes while the fetus was still in utero. Inspection of the f-QRS in utero and the newborn QRS shows marked similarity.

Examples of the f-QRS in breech presentation may be seen in Fig. 4. When the fetus presented by the breech, the f-QRS was directed oppositely to the f-QRS in vertex presentations, and, as might be expected, the fetal and maternal complexes were in the same direction. In Fig. 5 the f-QRS associated with a breech presentation in utero is shown above, and for comparison the newborn electrocardiogram with similarly placed electrodes is shown below. The parallelism is striking.

An interesting example of rotation from breech to vertex presentation is seen in Fig. 6. This patient had been followed for weeks during the gestation and had consistently shown the typical breech f-QRS illustrated in the upper tracing obtained at the thirty-ninth week. The next week, a few days before the

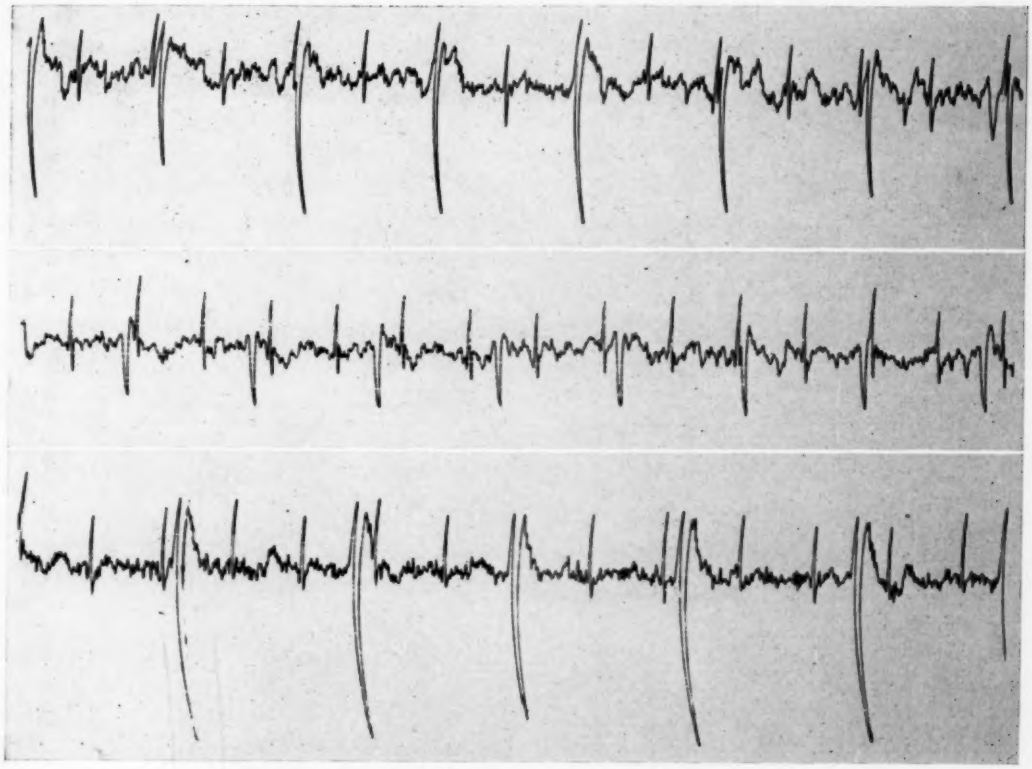

Fig. 1.—Normal fetal electrocardiogram from three different subjects, with the fetus in vertex presentation. Longitudinal leads. Maternal complex is seen to be directed down, and the fetal complexes are directed upward and occur at a faster rate.

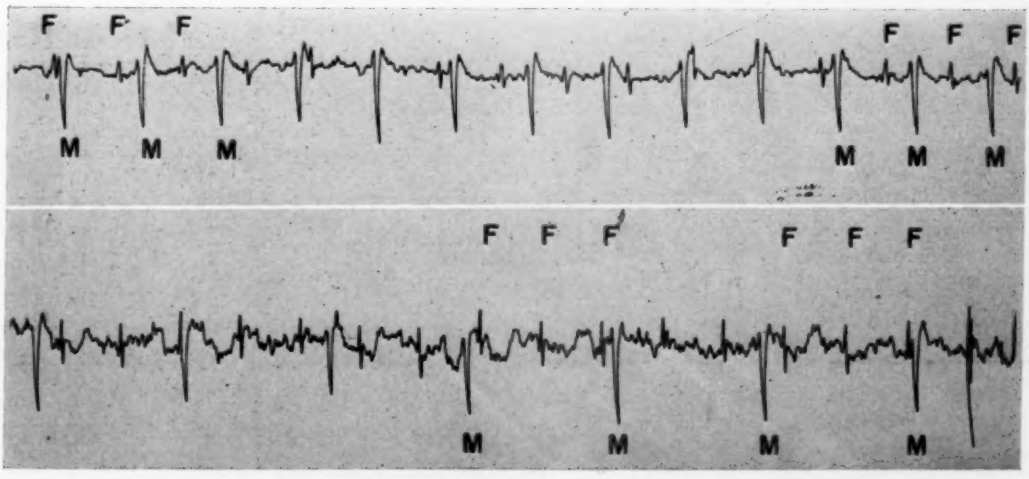

Fig. 2.—Appearance of the fetal electrocardiogram with differing relative fetal-maternal rates. Upper tracing shows fetal and maternal rates which are similar, largely because of a fast maternal rate. Lower tracing shows appearance with a slow maternal rate. On occasion, three fetal complexes can be seen in the interval between two maternal complexes.

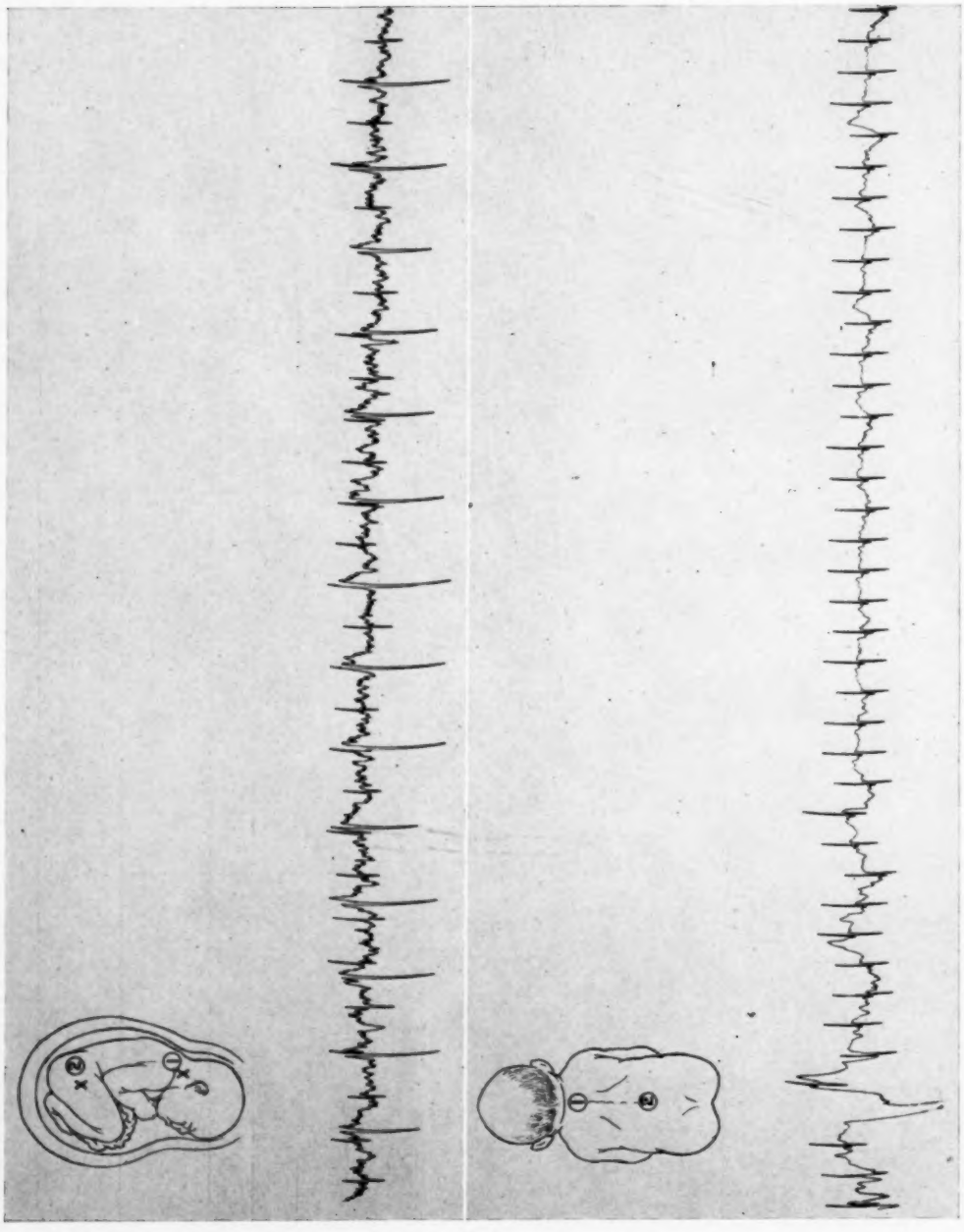

Fig. 3.—Comparison of the fetal electrocardiogram in utero with the newborn electrocardiogram. Vertex presentation. Upper tracing, the fetal electrocardiogram 10 minutes before delivery. Lower tracing, the newborn ECG 5 minutes after delivery. Every effort was made to place electrodes in comparable positions. The complexes are identical before and after delivery.

subject was scheduled for cesarean section and 2 days before the expected date of confinement, the f-QRS showed the typical pattern of vertex f-QRS. Clinical examination confirmed the presence of vertex presentation.

The earliest positive fetal electrocardiograms recorded in this series have been at 11½ weeks, following the presumed date of conception. Several such positive findings have been made, with some questionably positive findings at 12 weeks. Fig. 7 shows the tracings from two patients at 11½ weeks of age. The fetal complexes are marked by the letter F. The fetal heart rate was slow, about 90 to 100 per minute. Consecutive recording of the fetal complexes was relatively rare.

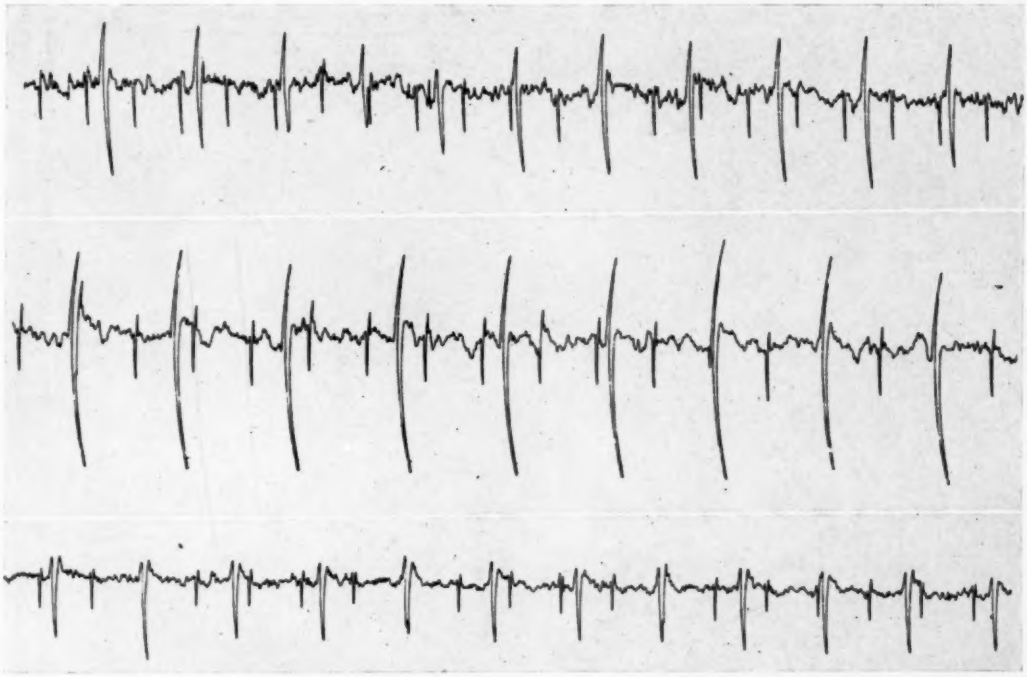

Fig. 4.—Fetal electrocardiogram in breech presentation, from three different subjects. The f-QRS is directed down, in contrast to the vertex presentations. Maternal and fetal complexes have the same primary direction.

It may be noted that the earliest complexes recorded were directed downward. In successive tracings, at weekly intervals, a shift in the f-QRS to the upward direction was ordinarily observed by the twenty-second week. Another result of interest was that in the interval between the seventeenth and twenty-second week, the f-ECG rather suddenly became very large, clear, and prominent, in many instances more so than in later pregnancy.

A comparison of the use of surface disk electrodes with the hand electrode is shown in Fig. 8. The three tracings were obtained from the same patient within a few minutes of each other. The upper tracing was obtained with the standard midline surface electrodes, and fails to show identifiable fetal complexes. With

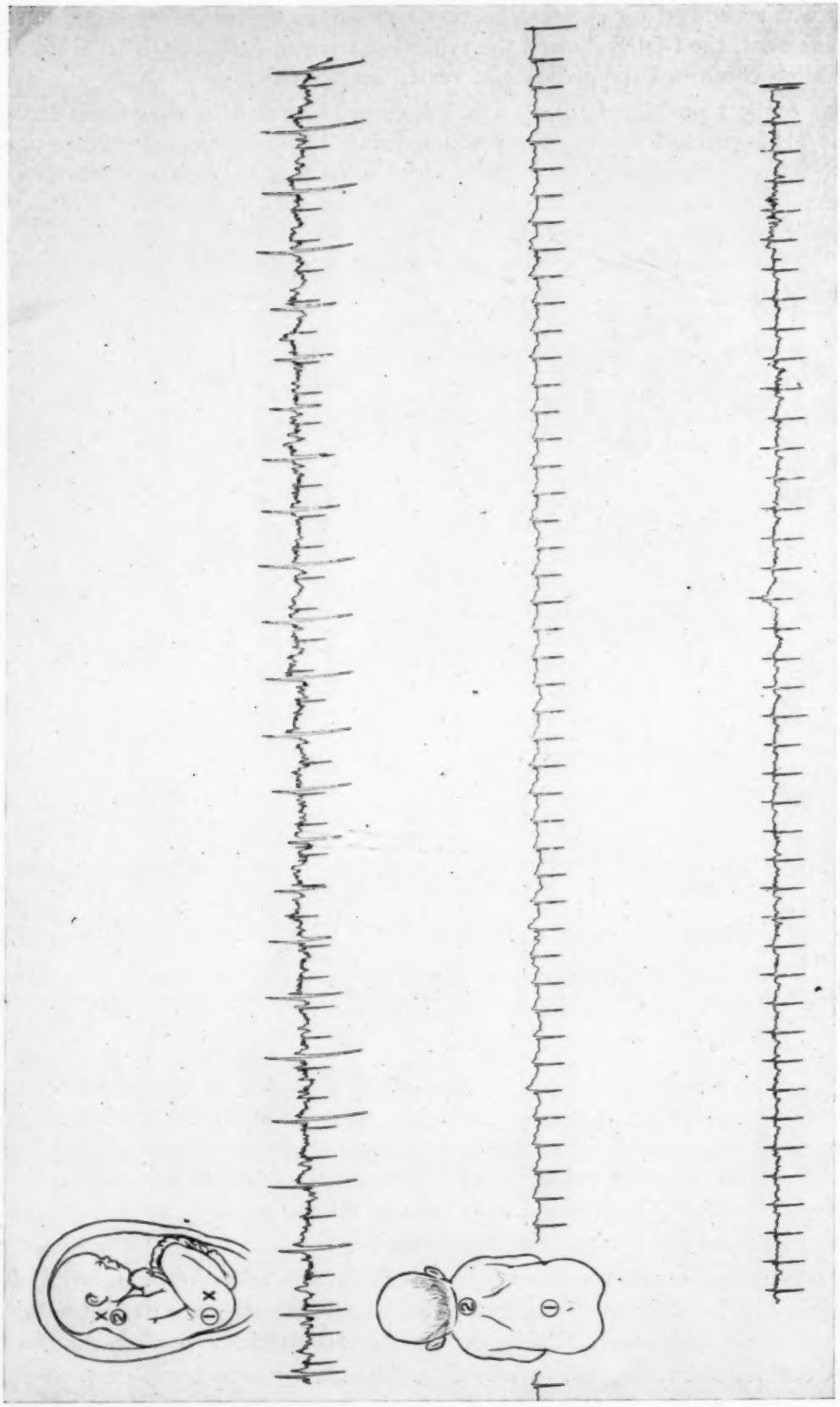

Fig. 5.—Comparison of the fetal electrocardiogram in utero with the newborn electrocardiogram, in a breech presentation. The complexes before and after delivery are very similar. Upper tracing, fetal electrocardiogram. Middle tracing, newborn electrocardiogram with electrodes similarly placed. Lower tracing, newborn standard Lead II.

the hand electrode in the same position a few moments later, large fetal complexes were obtained (middle tracing). A successive tracing at higher amplification is shown below.

In Fig. 9 are shown recordings from four different sets of twins. If the third tracing is taken as an example, it may be observed that, in addition to the large maternal complexes labeled M, there were two different kinds of fetal complexes occurring repetitively. One was a downward directed f-QRS labeled as F_1, the other was an upward directed complex labeled as F_2. The F_1 waves can be traced through the record independently, as can the F_2 complexes, and it may be

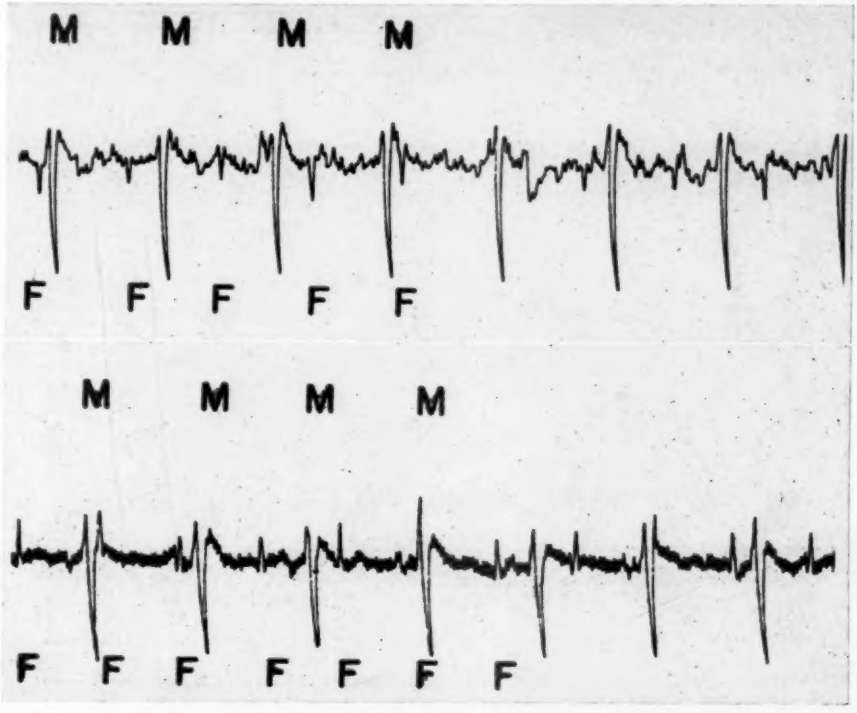

Fig. 6.—Rotation from breech to vertex at term, as indicated by the fetal electrocardiogram. The recordings are 1 week apart, and in each instance the position of the fetus was confirmed clinically. Upper tracing, breech indicated; lower tracing, 1 week later, vertex presentation indicated.

observed that the rates of the two fetal hearts were slightly different. The different directions of the two fetal complexes suggested that one twin was presenting as a vertex and the other as a breech, and this was corroborated by clinical examination. The difference in the fetal rates results in the fetal complexes approaching each other and then seemingly receding, a beating phenomenon rather characteristic of wave motions of slightly differing rates. This factor facilitates the identification of twins. In the lowest tracing, because of electrode placement, both of the large complexes were of fetal origin, the maternal complex M being relatively small.

In Fig. 10 may be seen an example of a diagnosis of multiple pregnancy made by fetal electrocardiography. All tracings were from the same patient, the uppermost at 16 weeks, and the second, third, and fourth tracings were at 21 weeks. On the basis of these tracings the diagnosis of multiple pregnancy was made at 21 weeks, and immediately confirmed radiologically. Actually, it is possible to make the diagnosis from the tracing of the sixteenth week.

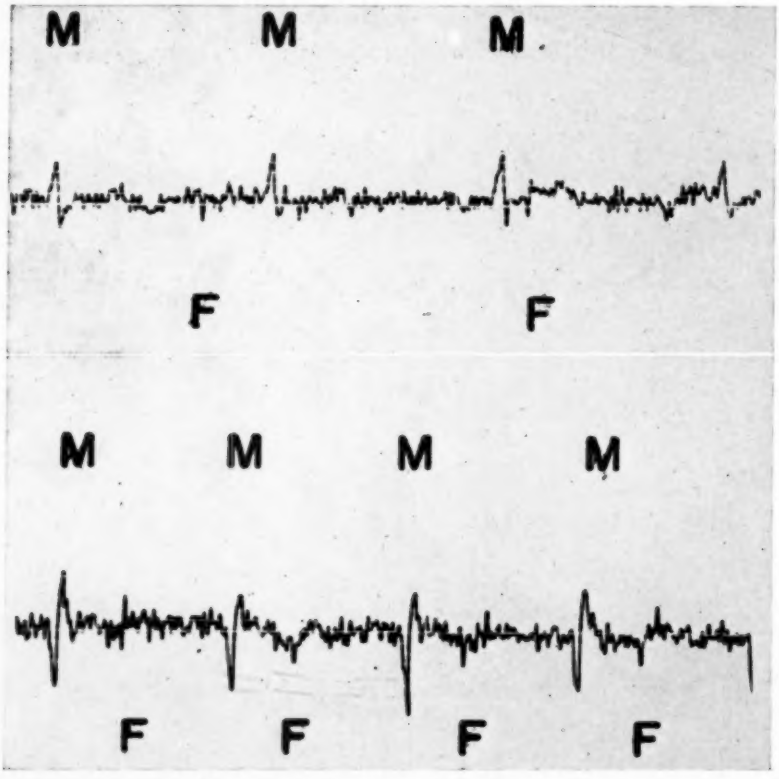

Fig. 7.—The early fetal electrocardiogram. Upper tracing shows two fetal complexes at 11 ½ weeks of embryologic age, with the fetal heart rate about 90 per minute. Lower tracing, also at 11 ½ weeks in another subject, shows several consecutive fetal complexes, with the rate about 100 per minute.

Fig. 11 shows an example of a demonstration of cardiac anomaly in utero. There were several unusual features in this tracing. First, the direction of the complex would seem to indicate a vertex presentation, yet x-ray evidence showed a breech. Second, the complexes were unusually wide and notched, suggesting conduction difficulties. Third, the complexes showed the prolonged overshooting which cardiologists usually refer to as S-T segment displacement. In this instance the infant showed delayed respiration at delivery and survived only 5 days. At autopsy, coarctation of the aorta was found.

It should be noted that, in general, it has been possible to demonstrate th fetal electrocardiogram from 2 to 6 weeks before the first auscultation of the fetal heart tones.

DISCUSSION

This investigation reveals that fetal electrocardiography can be a useful tool. Our experience indicates that in vertex presentations the f-QRS is upward, and in breech presentation it is downward. This is quite reasonable, since in breech presentations the electrical axis of the fetal heart is in the same general direction as that of the maternal heart. Hence, the fetal and maternal complexes should be in the same direction and should resemble each other. The opposite is true for the vertex presentations, since in these the fetal heart electrical axis is directed upward and to the right, while the maternal vector is to the left and down, so that the fetal complex should be 180° out of phase with the maternal complex.

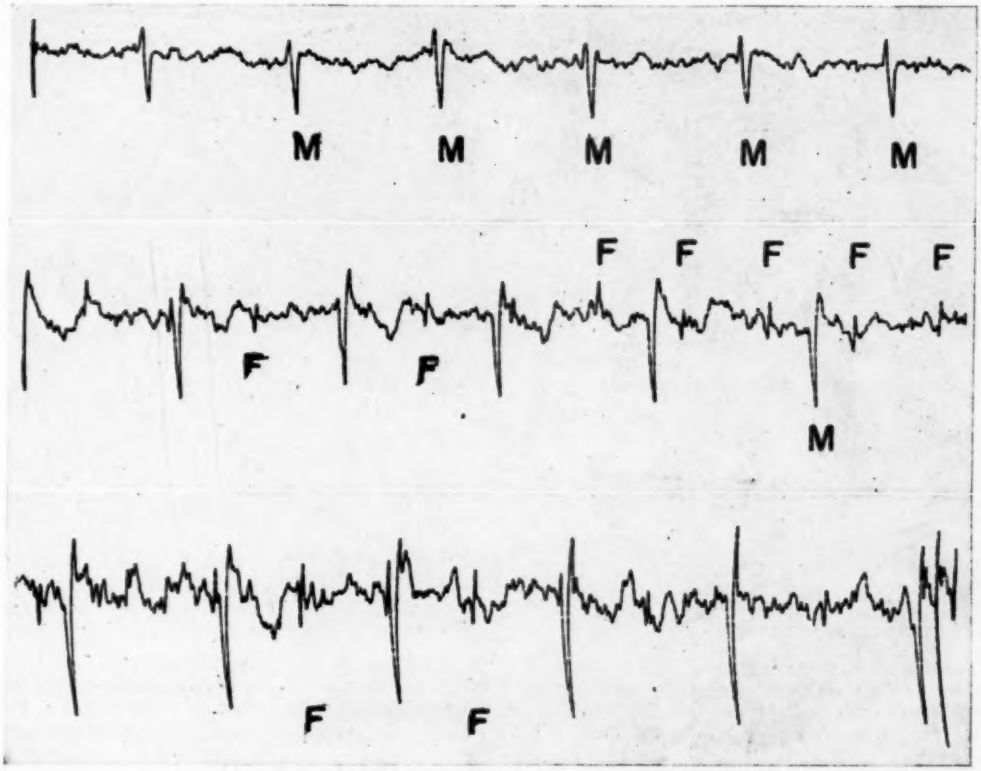

Fig. 8.—Comparison of results with the surface electrodes and with the hand electrode. Upper tracing, with surface electrodes; no fetal complexes can be demonstrated. Second and third tracings from the same patient, the same hour, using the hand electrode at two levels of amplification; the feta electrocardiogram may be seen clearly.

It should be possible to diagnose transverse or nearly transverse presentations by the use of horizontally orientated electrodes, and, indeed, to determine by the direction of the complex whether the fetal head is to the right or left. Fig. 12 explains the significance of the f-QRS deflections in determining the position of the heart and, thus, the position of the fetus.

On occasion, close to or during delivery, when it was difficult to hear the fetal heart tones, it has been possible to show a clear fetal electrocardiogram which was reassuring.

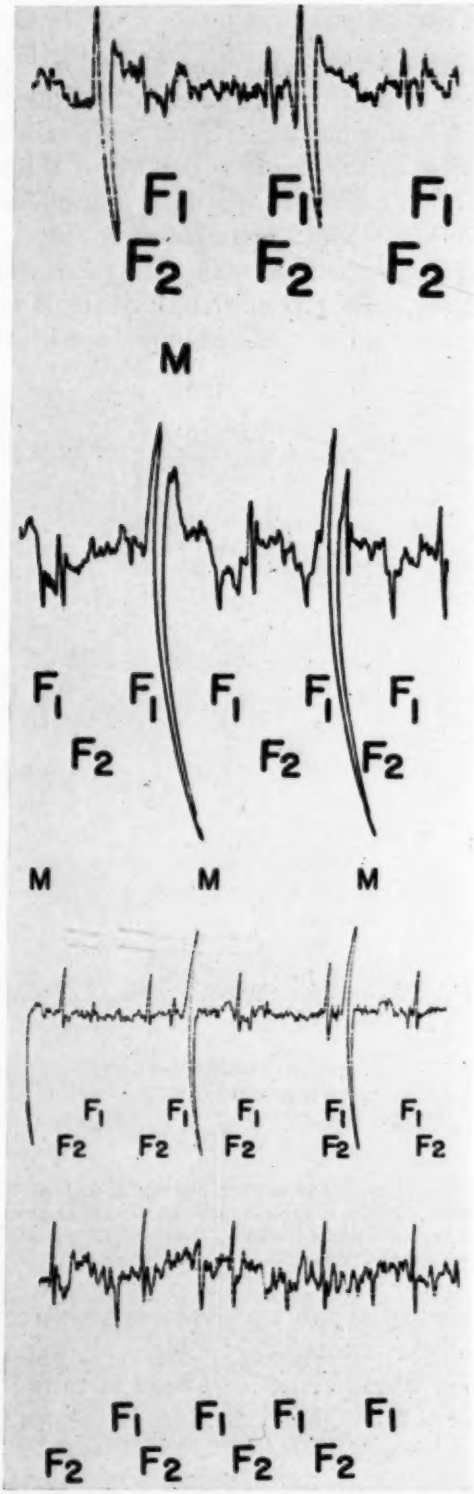

Fig. 9.—The fetal electrocardiogram in multiple pregnancy: four different sets of twins. In each instance the presence of twins was demonstrable radiologically, and viable twins were delivered. In the lowest tracing the original diagnosis of twins was made by the fetal electrocardiogram at 21 weeks.

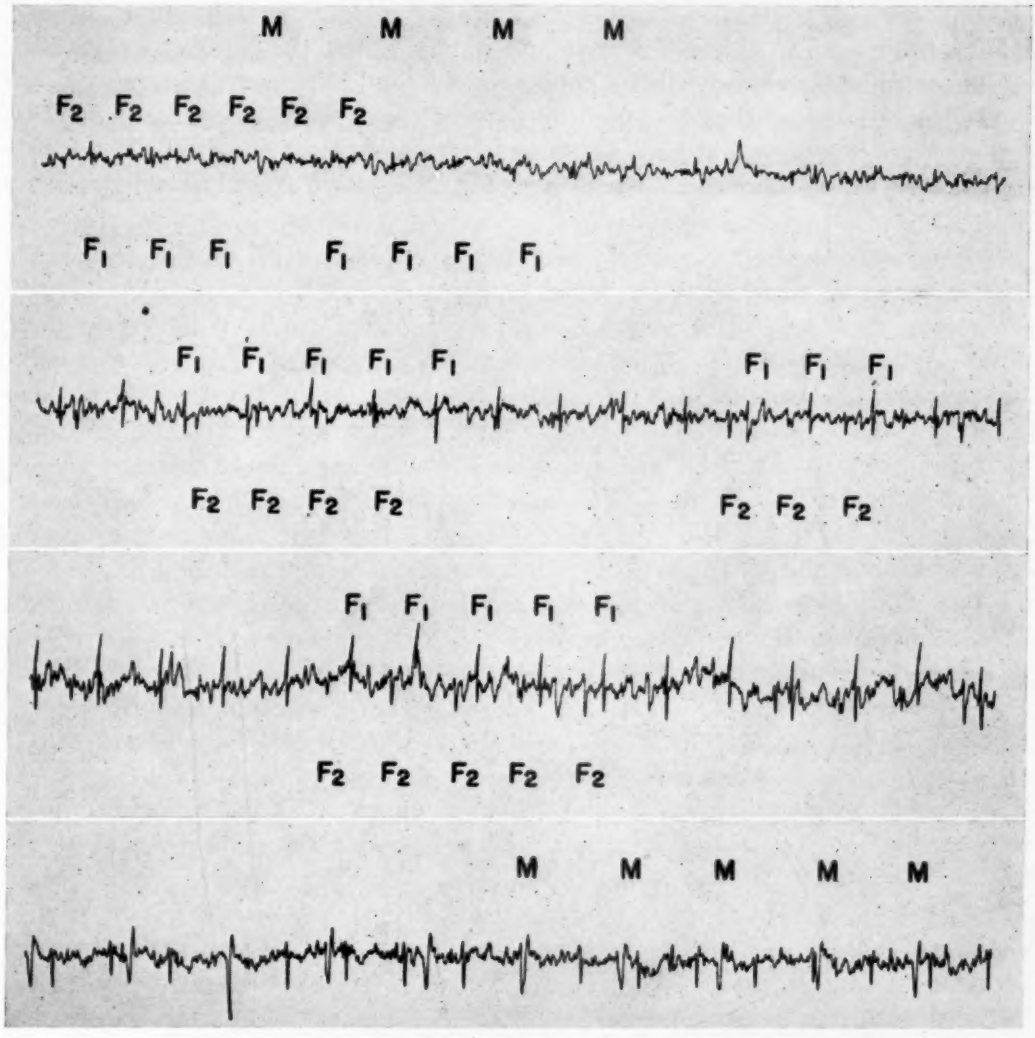

Fig. 10.—The same case as that in the lowest recording of Fig. 9. The top tracing is at 16 weeks, and the second, third, and fourth tracings at 21 weeks in the same patient. Inspection of the upper record shows that the diagnosis of twins can be made in the record of the sixteenth week. The lowest tracing is reproduced to show the maternal rate, using a different position of the electrodes.

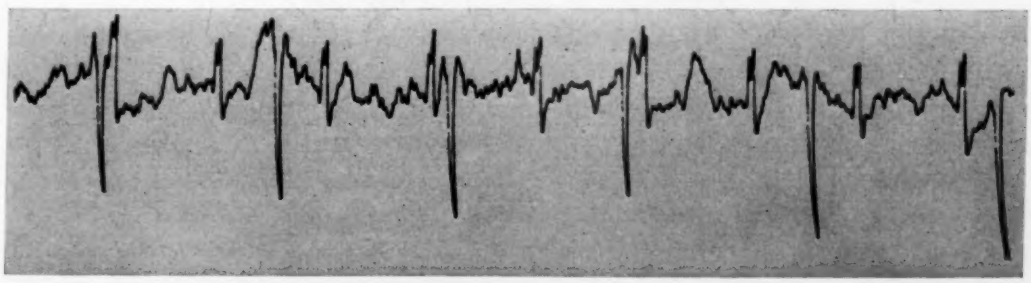

Fig. 11.—Cardiac anomaly as indicated by the fetal electrocardiogram in utero, near term. The f-ECG shows a wide and notched f-QRS, with S-T segment displacement. The direction of the main complex is upward, although the fetus was shown radiologically to be a breech presentation. The infant showed respiratory distress, and survived only 5 days.

The very clear relationship between the fetal electrocardiogram in utero and the newborn ECG should resolve any doubts about the significance of the complexes which have come to be known as the fetal electrocardiogram.

It has been noted that between the sixteenth and twenty-second weeks the fetal electrocardiogram first becomes large, sharp and clear, in certain instances more so than in later months. The reasons for the relative ease of demonstration

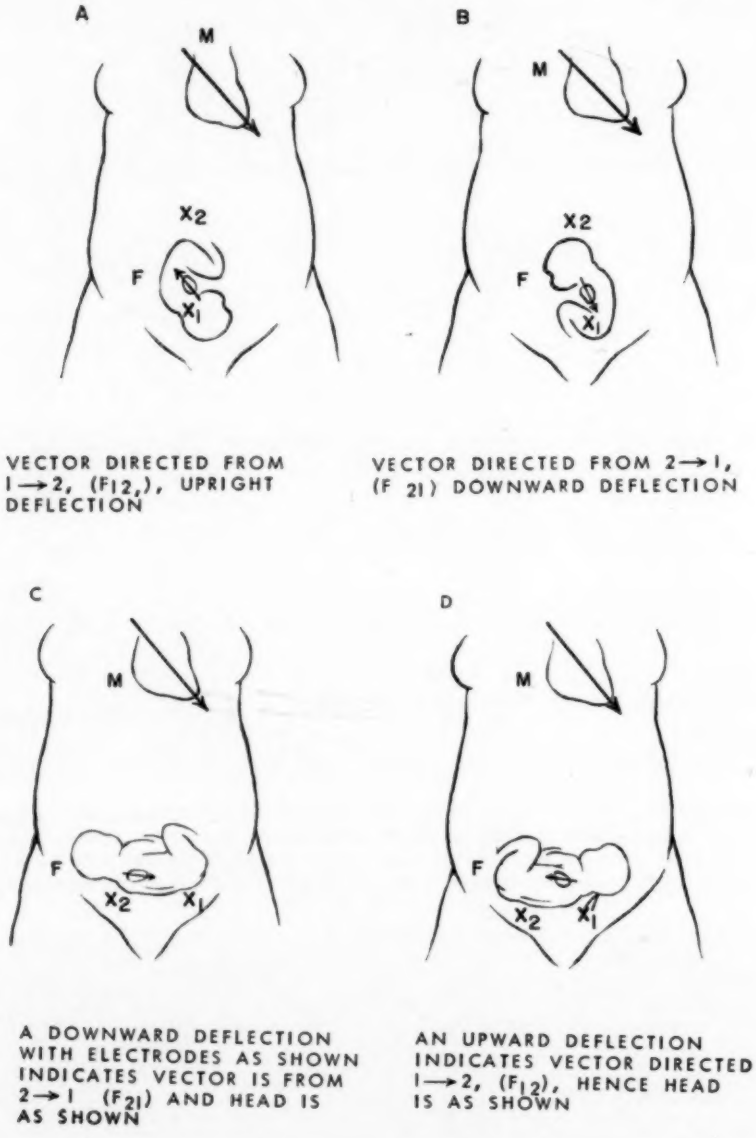

Fig. 12.—Utilization of the f-QRS direction in longitudinal and transverse leads for information as to the presentation of the fetus and the position of the fetal head. In *A* (vertex presentation) the electrical axes of maternal and fetal hearts are 180° out of phase, so that the maternal and fetal complexes should be oppositely directed. In *B* (breech presentation) the principal components of maternal and fetal electrical axes are in phase, so that the complexes should be in the same direction. In *C* and *D* the information thus derived is used to indicate the position of the fetal head in transverse presentations.

at this time are not yet known. However, at this time and afterward the f-ECG may become of diagnostic importance. The successful diagnosis of multiple pregnancy at 16 and 21 weeks, referred to earlier, may be used as an example. It should be possible to diagnose multiple pregnancies in general in this very simple way, without the risks entailed in exposure to radiation.

The earliest fetal complexes recorded in this series, at 11½ to 15 weeks, are directed downward. Judging by the consistent relationship which has been observed between such complexes and breech presentations at later stages of gestation, when clinical or radiologic evidence is available, it would seem that, ordinarily, the fetus presents by the breech at this early period of pregnancy. Similarly, the fact that the f-QRS changes to an upright complex in the usual case at about 20 weeks suggests that rotation to the more common vertex presentation takes place at about this time. It is possible, however, that a combination of rotation about two axes, not only the transverse but also the longitudinal axis of the fetus, might make changes in the f-ECG which could resemble breech-to-vertex rotation.

Studies of the early fetal electrocardiogram can make possible useful contributions to the knowledge of early cardiac development and, thus, help to bridge the gap between embryology and obstetrics. The fact that the fetal ECG is demonstrable some weeks before the fetal heart tones can first be heard is in itself a useful finding.

Much interest attaches to the demonstration of cardiac anomaly in utero, as reported above. It might well be possible to demonstrate such anomalies at the twentieth week, unless in certain instances damage takes place later. Congenital defect should be demonstrable, and perhaps special preparation might be indicated in such cases at delivery.

It should be noted that in instances where the viability of the fetus is in doubt, a positive f-ECG is certain and definite. A negative finding, however, does not have meaning, since in a small proportion of cases difficulties have been encountered in demonstrating the f-ECG in the presence of a living child. Further improvement of technique may remove this problem. It should also be noted that a negative finding in early gestation is without significance.

SUMMARY

1. Fetal electrocardiography, utilizing presently available instruments and technique, can demonstrate large, clear, definite complexes, and thus may be a valuable diagnostic aid in obstetrics and allied fields.

2. The f-ECG is shown to provide rapid information as to the presence of a living fetus, and its presentation.

3. Recordings from four sets of twins are shown, indicating the value of fetal electrocardiography in cases of multiple pregnancy.

4. Diagnosis of multiple pregnancy at 16 and 21 weeks is demonstrated.

5. Recording of the fetal electrocardiogram in utero, and subsequent electrocardiograms of the newborn are shown for both vertex and breech presentations. The identity of the complexes is beyond doubt.

6. It is shown that an early diagnostic period exists at 16 to 22 weeks, at which time diagnosis of cardiac anomaly and multiple pregnancy should be possible.

7. A demonstration by fetal electrocardiography of a case of cardiac anomaly is presented, in which coarctation of the aorta was found at autopsy. The fetal electrocardiogram in this instance was clearly abnormal, with a wide, notched QRS and S-T displacement.

8. Fetal electrocardiography provides positive results from 2 to 6 weeks earlier than auscultation of fetal heart tones.

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Electrocardiographic Interrelationship of the Pre-Excitation (Wolff-Parkinson-White) Syndrome and Myocardial Infarction

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INTRODUCTION

Previous reports have demonstrated that the presence of the pre-excitation phenomenon (Wolff-Parkinson-White syndrome) can both simulate and mask the electrocardiographic signs of myocardial infarction.[1-5] It has been pointed out that deformity of the QRS complex and the J-T segment either may reflect the pre-excitation alone or may represent changes due to myocardial infarction superimposed on those related to the conduction abnormality.[1,3,6-8] It has been also pointed out that the occurrence of complexes with normal pathways of ventricular depolarization may definitely establish the presence of myocardial infarction in patients whose pre-excitation is intermittent.[1,2,8] The case described in this report demonstrates each of these relationships.

CASE REPORT

The patient, a 44-year-old Negro, was admitted to Bellevue Hospital in November, 1955, because of chest pain. Thirteen years earlier, following a brief hospitalization for pneumonia, he noted the onset of episodic palpitations which subsided spontaneously. These recurred with increasing frequency up to the time of admission. One year prior to admission he noted the onset of retrosternal pain which occurred on exertion and was relieved by rest. He visited a physician who told him that he had high blood pressure. No electrocardiogram was obtained and no therapy was advised. His anginal attacks persisted and he changed his job to one requiring less exertion. Six hours prior to admission he was aroused from sleep by severe, crushing anterior chest pain.

On admission his blood pressure was 190/110 mm. Hg. Physical examination revealed scattered retinal hemorrhages, with arteriolar narrowing and cardiomegaly. There was 3+ albuminuria, a blood urea nitrogen of 19 mg. per cent, and a serum cholesterol of 290 mg. per cent. An electrocardiogram showed sinus rhythm with Wolff-Parkinson-White syndrome. During the first 72 hours his temperature rose from 99° F. to 101.2° F., and his white blood count from 8,500 to 11,000, but both subsided to normal by the fourth hospital day. The erythrocyte sedimentation rate by the Wintrobe method was 40 mm. in 1 hour on admission and fell to 28 mm. on the fourth hospital day.

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The patient was treated with bed rest and anticoagulants, and following an uneventful convalescence, he returned to work with only mild restriction of activity imposed by persistent angina.

DISCUSSION

Analysis of the electrocardiograms obtained throughout this patient's hospitalization afford an opportunity to review many of the previously reported interrelationships between the electrocardiographic manifestations of the pre-excitation syndrome and those of myocardial infarction. The patterns of evolution of myocardial infarction are both exaggerated and simulated by alterations of the configuration of the QRS complexes produced by variations in the degree of pre-excitation. Changes due only to myocardial infarction are also demonstrated in the face of this conduction disturbance.

The electrocardiogram obtained on the seventh hospital day (Fig. 1), recorded during a period of normal atrioventricular conduction, shows the pattern of an inferoposterior myocardial infarction. This record together with a sagittal vectorcardiogram obtained at a later date present definite electrical evidence

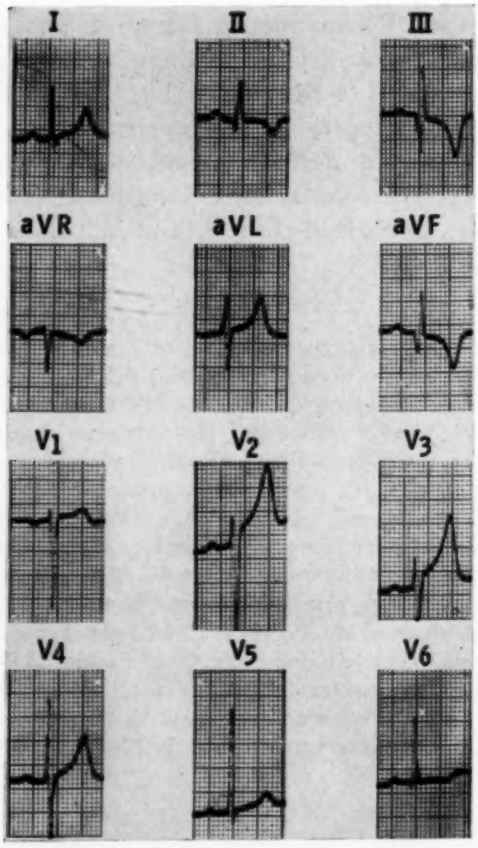

Fig. 1.—Electrocardiogram taken on the seventh hospital day, which reveals a normal atrioventricular conduction with the pattern of an inferoposterior myocardial infarction. Note the tall peaked T waves in Leads V_2 to V_4, indicating involvement of the posterior wall.

of the prior occurrence of this infarction.[9-11] Each of the electrocardiographic manifestations of this infarction—i.e., the Q in Leads III and aV_F, the coved, inverted T waves in those leads, and the tall peaked T waves in the precordial leads—are altered in various ways in each of the other electrocardiograms, all of which show varying degrees of the pre-excitation phenomenon.

A Q wave is recorded in Leads III and aV_F in all of the records obtained. In the record which shows no pre-excitation, this initial infarction vector has a duration of 0.04 second, and the spatial vector is then abruptly directed inferiorly and anteriorly. The continued superior orientation of the QRS vector (QS pattern in Lead aV_F) in those records with varying degrees of pre-excitation (Fig. 2) demonstrates clearly that the wave of depolarization in the prematurely and aberrantly depolarized tissue exaggerates the pattern of infarction.[13] Since pre-excitation alone may produce a Q wave in Leads III and aV_F,[1,4] even the initial 0.04-second vector in these records may reflect the pre-excitation phenomenon and may be totally independent of the infarction. This possibility emphasizes the importance of electrocardiograms which do not show any pre-excitation when one is attempting to make an electrocardiographic diagnosis of

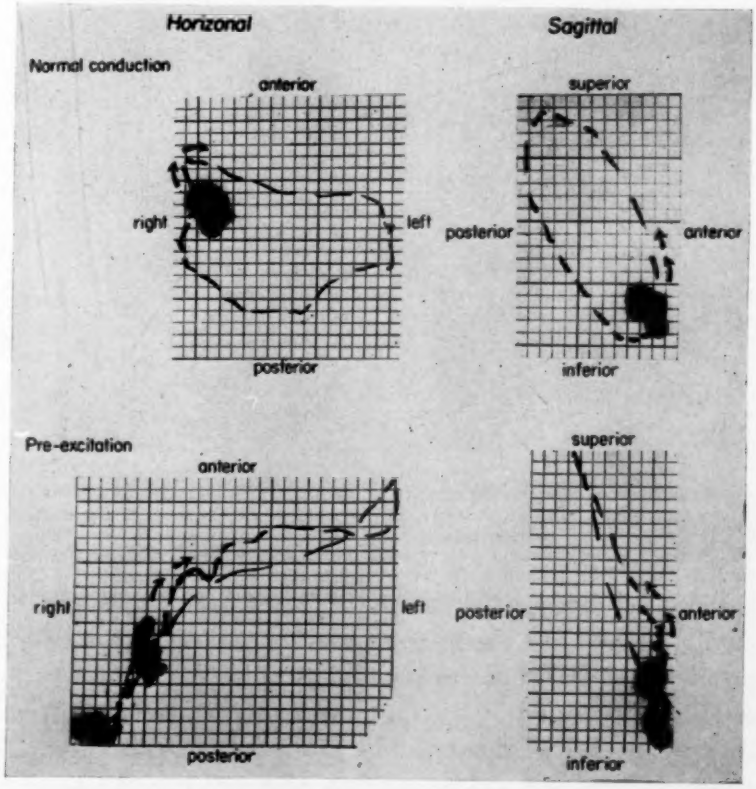

Fig. 2.—Vectorcardiograms showing the change in the spatial loop when the pre-excitation phenomenon is present. *A*, When normal conduction is recorded, the loop is directed initially superiorly, and then inferiorly. Note the absence of significant delay in any part of the tracing. *B*, During a period of pre-excitation the initial direction is again superior, but the conduction delay is evident from the proximity of the initial dots. The loop remains superiorly oriented throughout its extent, accounting for the QS pattern noted in Lead aV_F in the electrocardiograms during pre-excitation.

myocardial infarction in patients with the Wolff-Parkinson-White syndrome.[1,2] The experimental production of myocardial infarction in animals with an artificial A-V connection demonstrates, however, that a sufficiently large area of necrosis can produce a Q wave in the presence of pre-excitation.[6]

It is well recognized that if the entire ventricular depolarization proceeds over abnormal pathways, the electrical record of the subsequent repolarization (J-T segment) will also be abnormal.[14] This is best demonstrated by the secondary T-wave alterations seen in left bundle branch block. In the pre-excitation syndrome the ventricular mass which is depolarized by the abnormal premature depolarization will be associated then with an abnormal wave of repolarization.

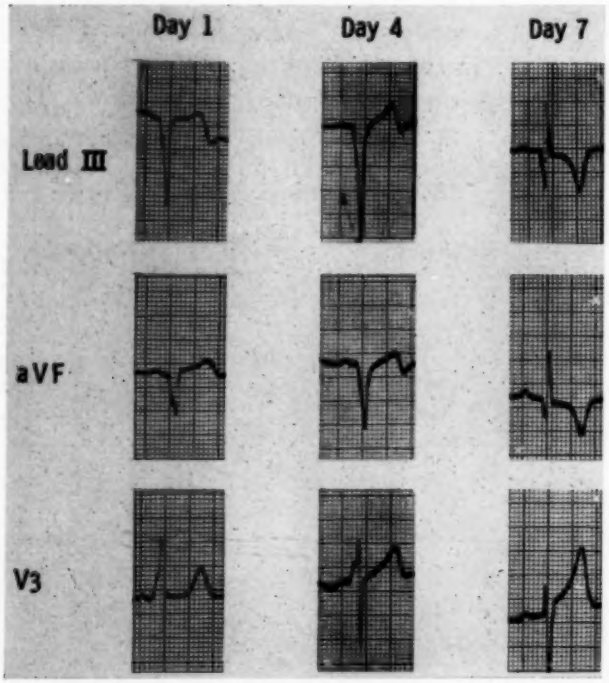

Fig. 3.—Selected leads from the electrocardiograms taken during the first seven days of hospitalization. Note the serial ST-T wave alterations, and the varying degrees of pre-excitation, which are best seen in Lead V_3. See text for further discussion.

Since it has been demonstrated that any pre-excitation complex is a composite of the contributions of the tissue depolarized prematurely and that depolarized through normal conduction pathways, the resulting J-T configuration will reflect the degree of pre-excitation.[6,12] At a given degree of pre-excitation a particular configuration of the J-T segment will be produced repeatedly.[6,15]

That this phenomenon, the production of serial alterations due only to variations in the degree of pre-excitation, can simulate that of the evolution of myocardial infarction is evident in this case. Fig. 3 shows, in chronological order, tracings taken during the first week of hospitalization. These were considered to demonstrate the evolution of an inferoposterior myocardial infarction. Analy-

sis of the electrocardiograms obtained subsequently shows clearly that most of this J-T segment alteration was related to the varying degrees of pre-excitation which they demonstrate, rather than to the evolution of the myocardial infarction. This is evident from the electrocardiograph in Fig. 4, obtained 32 days after admission. This record resembles that obtained on the fourth hospital day. Since this record shows less "evolution" of the infarction pattern than does the record obtained on the seventh hospital day, the original changes in the J-T segment almost certainly represent changes secondary to the degree of pre-excitation, and not those due to tissue injury.

This patient does demonstrate, however, J-T segment alterations which are reflections of myocardial change, unrelated to the pre-excitation phenomenon. In the experiments of Tamagna[6] the pattern of myocardial injury was reflected in J-T segment alterations in tracings showing the same degree of pre-excitation.

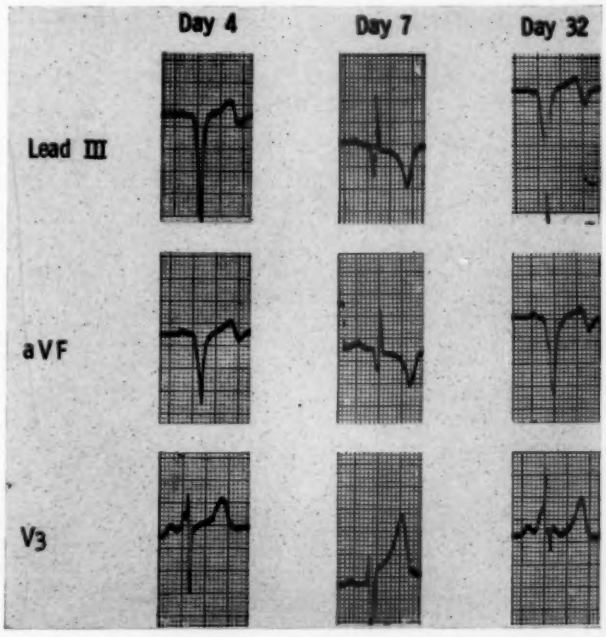

Fig. 4.—Selected leads from records obtained on the fourth, seventh, and thirty-second hospital days. Note that the J-T segment of the latest tracing more closely resembles the record obtained on the fourth hospital day (a record showing a comparable degree of pre-excitation) than it does the record taken on the seventh hospital day (a record showing no pre-excitation phenomenon). See text for further discussion.

This indicates that changes due to myocardial disease can be superimposed upon, and can emerge through, those J-T segment alterations secondary to the pre-excitation. Fig. 5 shows records of approximately the same degree of pre-excitation as determined by the P-R and QRS intervals. These two records were taken on the fourth and twenty-sixth hospital days and demonstrate definite ST-T wave alterations. These changes must be related to tissue damage, since approximately the same degree of pre-excitation obtains in each.[6,15] That this ST-T wave progression is the result of myocardial disease is also evidenced by

the marked change in the QRS-T wave angle, estimated in the frontal plane. Although the demonstration of myocardial infarction in this patient is unequivocal, the relationship to this infarction of the demonstrated ST-T changes is unclear. The deeply coved T wave in Lead aV_F which was demonstrated on the seventh hospital day when there was no pre-excitation suggests that this infarct may have occurred prior to this clinical episode. The T-wave changes demonstrated on subsequent records with similar degrees of pre-excitation could indicate a separate area of tissue injury.

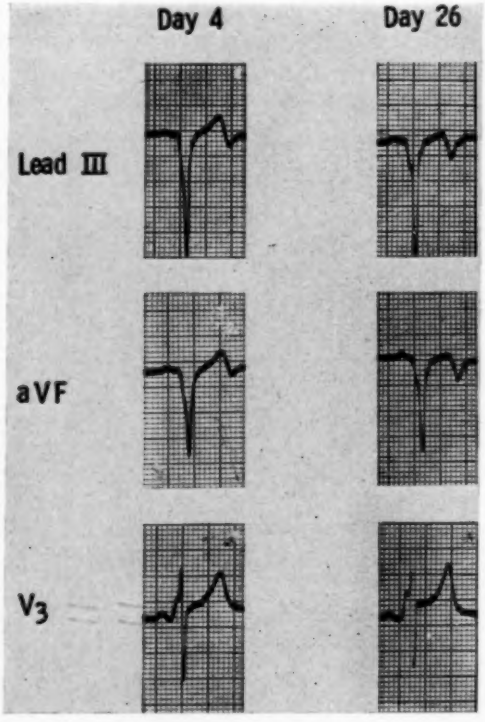

Fig. 5.—Selected leads from records obtained on the fourth and twenty-sixth hospital days. Note that although comparable degrees of pre-excitation are present, alteration in the ST-T wave has occurred, indicating myocardial change independent of alterations in conduction.

Since no electrocardiograms obtained prior to this hospitalization are available, the possibility exists that the pre-excitation phenomenon demonstrated in this patient is a result of the myocardial infarction.[16] The history of previous episodes of tachycardia, however, strongly suggests the presence of pre-excitation prior to hospitalization.

SUMMARY

A case is presented in which electrocardiographic evidence of myocardial infarction is demonstrated in a patient with intermittent pre-excitation (Wolff-Parkinson-White) syndrome. It has been shown in this case that the QRS

complex of pre-excitation phenomenon can both simulate and mask that of myocardial infarction, and that J-T segment alterations can be due to either or both when these two conditions co-exist.

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The Origin and Interpretation of Murmurs in Coarctation of the Aorta

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At the present time the murmurs of coarctation of the aorta are regarded as giving little information beyond a clue to the cause of one form of hypertension. They are usually described, according to Reifenstein, Levine and Gross,[1] simply as systolic murmurs heard over the precordial region, especially below the left clavicle, and often at the back between the scapulae. These authors flatly stated that "a diastolic murmur is not found in uncomplicated coarctation of the aorta." Diastolic murmurs which have been reported are regarded, generally, as not being due to coarctation, but as coming from complicating lesions such as a patent ductus arteriosus, or aortic vavular insufficiency. This latter functional diagnosis is then often ascribed to a bicuspid aortic valve because of the statistical prominence of this anomaly in coarctation. White[2] makes the clearest clinical description of variations in the systolic murmurs, describing "long systolic murmurs" and "in some cases a continuous murmur, not continuing throughout all diastole, can be well heard over the thoracic spine." However, he does not indicate the source of the systolic and the diastolic components of the murmur. Wells, Rappaport and Sprague[3] show phonocardiographic tracings of diastolic murmurs and regard them, when heard anteriorly, as evidence of aortic valvular regurgitation. They conclude, however, because of the frequent posterior distribution, that "both systolic and diastolic murmurs are frequently present in uncomplicated coarctation of the aorta." Spencer and Denison[4] have recently reported that a continuous murmur is produced in the aorta when the isthmus is severely stenosed by both congenital and experimental coarctation.

The purpose of this paper is (1) to point out two separate hemodynamic sources of systolic murmurs in uncomplicated coarctation, (2) to identify a diastolic, high-pitched, diminuendo murmur as actually a part of a continuous crescendo-decrescendo murmur arising from the aorta, (3) to demonstrate a

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useful relationship between the severity of stenosis and clinically recognizable variations of the aortic murmur, (4) to establish a basis for differentiation of murmurs of aortic stenosis and aortic regurgitation from those of coarctation of the aorta, (5) to present an esophageal auscultatory technique, from which one may predict the position and severity of the stenosis, and (6) to present a method of study of murmurs which utilizes the measurement of the blood flow responsible for the murmur.

METHODS

Twenty consecutive patients admitted to North Carolina Baptist Hospital with congenital coarctation of the aorta were studied before, during, and after surgical resection of the stenosed segment. In addition, the thoracic descending aortae in 25 dogs were experimentally constricted as a means of producing acute graded experimental coarctation.

1. Murmurs in the patients were studied pre- and postoperatively by (1) auscultation of the chest wall (a) with a stethoscope and (b) by means of a Sanborn heart sound microphone, and (2) auscultation from the esophagus by means of a catheter-tip barium-titanate microphone. During surgery the murmurs coming from the aorta and collateral channels were studied (1) by means of a sterile stethoscope applied directly to the aorta and collateral channels, and (2) by means of a barium-titanate phonocatheter directly from the thoracic vessels and heart as well as from a second barium-titanate phonocatheter in the esophagus.

The Ampex 350 tape recorder was used to amplify and record when the phonocatheters and microphones were used. Permanent records were made on tape and transcribed with the Hathaway S14E optical oscillograph. The murmurs were accentuated for illustrative purposes by means of band-pass twin-T network filters. Essentially the same sound techniques were used on the experimental animals. For the purposes of this paper, systole is defined as the interval between the beginning of the first sound and the beginning of the second sound.

2. Blood flow pulsating through the site of the coarctation segment was measured by means of the surgical probe type, square-wave magnetic flowmeter.[5-7] This method essentially consists of a waterproof, plastic-enclosed electromagnet applied directly to the unopened aorta or collateral channels. The flow of blood within the magnetic field generates a voltage proportional to the volumetric rate of flow. Magnets of various sizes were built so that the vessel under study could be matched without undue compression. The validity and safety of this method of blood flow measurement in the operating room has been established.[6,8] Since the square-wave magnetic flowmeter was used as a pulsatile flowmeter, it was possible to correlate the phasic changes in the velocity of flow with changes in intensity and duration of the murmurs arising at the point of study.

3. Arterial pulsatile pressure was measured in many patients by means of a Statham P23D transducer attached by way of a 30-cm. length of polyethylene tubing and a needle tip inserted into the aorta. The standard auscultatory technique for brachial arterial pressure was also employed in all patients. In the experimental animals the aortic pressure was measured by means of a cannula introduced through the carotid artery.

The graded experimental stenosis was produced in the dogs' isthmal aortae by means of a wire loop passed around the aorta and tightened by pulling one free end through a small tube whose end lay against the outside wall of the vessel. The original internal circumference was estimated by the following procedure: First, the wire loop was pulled up until the aorta was encompassed exactly but without compression. A point of reference was made between the free end of the wire and a millimeter rule attached to the tube. The wire was then tightened on the aorta until the lumen was occluded, as indicated by complete cessation of the murmur. The difference in millimeters between the position of the end of the wire at the point of complete occlusion and its original point of reference represented the internal circumference of the vessel. By assigning values to each of the intervening millimeter marks, the internal circumference during any degree of partial occlusion could be read off directly. This method assumed a constant wall thickness, which may not be exactly correct. This deficiency, however, is minimal at those severe

degrees of constriction which are seen most commonly in congenital stenosis, and which also represent a range of the most critical changes in hemodynamics. The experimental arrangement is diagrammed in Fig. 1.

In congenital coarctation the internal diameter (i.d.) of the orifice at the point of coarctation was measured from the resected specimen. This measurement may have been in error by being smaller than the in situ diameter, but no better method was found. Experience in examining the resected specimens indicated that error from estimating the orifice size in this way was probably greatest in the younger individuals, in whom the aorta had greater elasticity.

In several experiments on the effect of hypertension on the blood flow and murmur a suture was tied about the vessel and constricted to a fixed degree. Upon sacrifice of the animal in this experiment the internal diameter at the point of constriction was measured by means of a tapered rod.

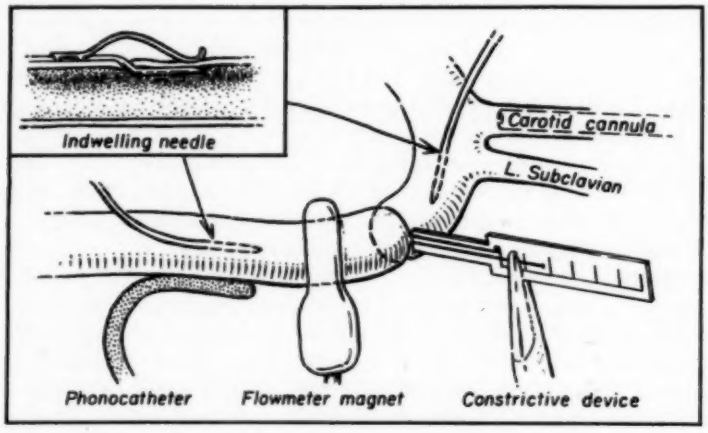

Fig. 1.—Composite diagram showing orientation of various measuring devices applied to the aorta. The indwelling clip-needle is designed to record true lateral pressure. In the patients with coarctation the flowmeter magnet was applied directly over the coarctation orifice.

RESULTS

A. *Congenital Coarctation.*—

The 20 patients varied in age from 8 weeks to 39 years; all were males except one girl, aged 1 year. In each, the stenosed segment was resected and the aorta anastomosed end-to-end without grafting. None of the patients had a patent ductus arteriosus. The coarctation was located just below the left subclavian artery in 18 patients, at the junction of the left subclavian in one, and just proximal to the subclavian in another. Complete obstruction of the aorta was found in 2 patients. The degree of stenosis found in the resected coarctation specimens is shown in Table I.

Systolic Murmurs on the Precordium.—Auscultation of the precordium before surgery always revealed a Grade 2 to Grade 3 systolic murmur, widely distributed over the thorax, usually loudest in the left infraclavicular area. This murmur characteristically began in early systole and extended into the second sound. Along the lower sternum and in the epigastrium it frequently displayed further shifting, beginning later in systole and ending beyond the second sound. The typical systolic murmur has no special quality; therefore, it is called "blowing." A soft whistle accompanied the systolic murmur at the apex in J. Ph., and at the

lower left sternal border in W. S. In Patients D. P. (Fig. 2) and W. S., a coarse, Grade 4 systolic murmur was heard over the aortic area and radiated into the neck. This murmur persisted undiminished after operation. A thrill was also present over the aortic area in D. P., pre- and postoperatively.

Diastolic Murmurs on the Precordium.—In W. S. and in G. Mc. a high-pitched Grade 1 diastolic murmur was heard along the left mid-sternal border, accentuated slightly with the patient in the sitting position and leaning forward in full expiration. This murmur was not present on the posterior chest wall. Its quality was typical of early aortic valvular regurgitation, and it persisted unabated after surgical resection of the coarctation segment. In D. L. a third heart sound was recorded at the apex.

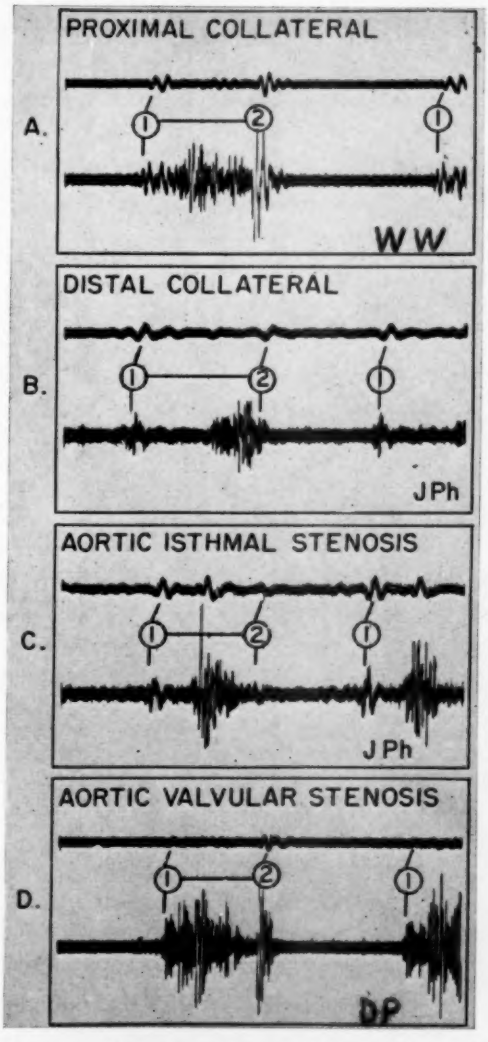

Fig. 2.—Systolic murmurs commonly found in coarctation of the aorta. In each case the upper tracing is of heart sound frequencies below 70 c.p.s., while the lower tracing is of murmurs with a 250 c.p.s. band-pass filter. *A*, From over the supraclavicular artery in patient W. W. *B* and *C*, From descending thoracic aorta before and after resection and reanastomosis of completely obstructed isthmus in Patient J. Ph. *D*, From aortic area, 1 week after repair of coarctation of the aorta, in Patient D. P.

TABLE I. THE RELATIONSHIP BETWEEN THE MURMUR IN THE DESCENDING AORTA AND THE DEGREE OF STENOSIS IN CONGENITAL COARCTATION

PATIENT	AGE (YR.) WEIGHT (LB.)	HEMATOCRIT OR HEMOGLOBIN	ADMISSION ARTERIAL B. P. (MM. Hg)	TECHNIQUE*	AORTIC MURMUR†			I. D. (MM.)	STUDY B. P. (MM. Hg)	DIASTOLIC AND CONTINUOUS MURMURS AT PHYSICAL EXAMINATION	
					1ST SOUND	2ND SOUND	1ST SOUND				
J.Ph.	23 206	15.2 Gm.	200/118	A	—			0	120/80	None	A.
D.E.	12 mo. 16	34%	150/80	E	NONE			0	150/80	None	
C.H.	30 135	44%	164/88	A	——	——	——	1	190/115	None	B.
J.C.	15 116	15 Gm.	160/110	A	——	——	——	<1	130/100	Continuous, faintly posteriorly	
W.P.	13 156	16.5 Gm.	155/95	O	——	——	——	2	175/115	Continuous anterior and posterior, coarse, loudest anterior	
J.D.G.	12 118	49%	170/75	O	——	——	——	2	170/100	Continuous, loud posteriorly	
G.C.	10 53	40%	150/100	A	——	——	——	2.5	160/100	None	
W.W.	7 50	38%	130/70	A	——	——	——	1	140/90	Continuous, faintly posteriorly	
L.N.	10 54	47%	186/118	A and E	——	——		1	180/100	Continuous posteriorly, and in esophagus	
M.L.	26 177	51%	180/100-94	A	——	——		<1	180/110	None	
D.L.	8 wk. 8 lb. 11 oz.	11 Gm.	118/?	A	——	-		1	—	None	
L.W.	35 170	14 Gm.	210/110	A and E	——			4	212/100	None	C.
W.S.	19 135	50.6%	180/60	A	——			3.5	170/90	Very faint, high pitched, diastolic, left sternum	
D.P.	17 110	16.2 Gm.	144/104	O	——			3	130/90	None	
P.R.	35 173	51%	150/80	A	——			6	130/80	None	
G.Mc.	39 137	14.2 Gm.	193/94	A and E	——			—	130/70	Very faint, high pitched, diastolic, left sternum	
J.M.	23 173	46%	134/82	A	——			4x7 (oval)	110/80	None	
J.B.	35 156	47%	140/90	A and E	——			6x8	108/76	None	
J.Pit.	10 65	37%	154/84-64	—				1	154/84-64	—	D.
B.L.	19 146	49%	180/84	—				2-3(?)	215/125	None	

*Techniques *A*, *E*, and *O* refer to whether the aortic murmur was recorded directly from the aorta (*A*), from the esophagus (*E*), or from the chest wall (*O*).

†The timing and duration of the aortic murmur is shown relative to the heart sounds by the length of the horizontal lines in the columns below.

A, Patients with complete obstruction. *B*, Patients with nearly complete obstruction. *C*, Patients with least obstruction. *D*, Patients in whom the aortic murmur was not recorded.

Continuous Murmurs on the Precordium.—In W. P. a loud continuous murmur (i.e., crescendo-decrescendo murmur with the same systolic and diastolic quality extending throughout the entire heart cycle and not hesitating at the second sound) was heard widely over the precordium, but was loudest in the left infraclavicular area. This murmur (illustrated in Fig. 3) was also clearly heard posteriorly between the scapulae; it completely disappeared after surgical resection of the coarctation.

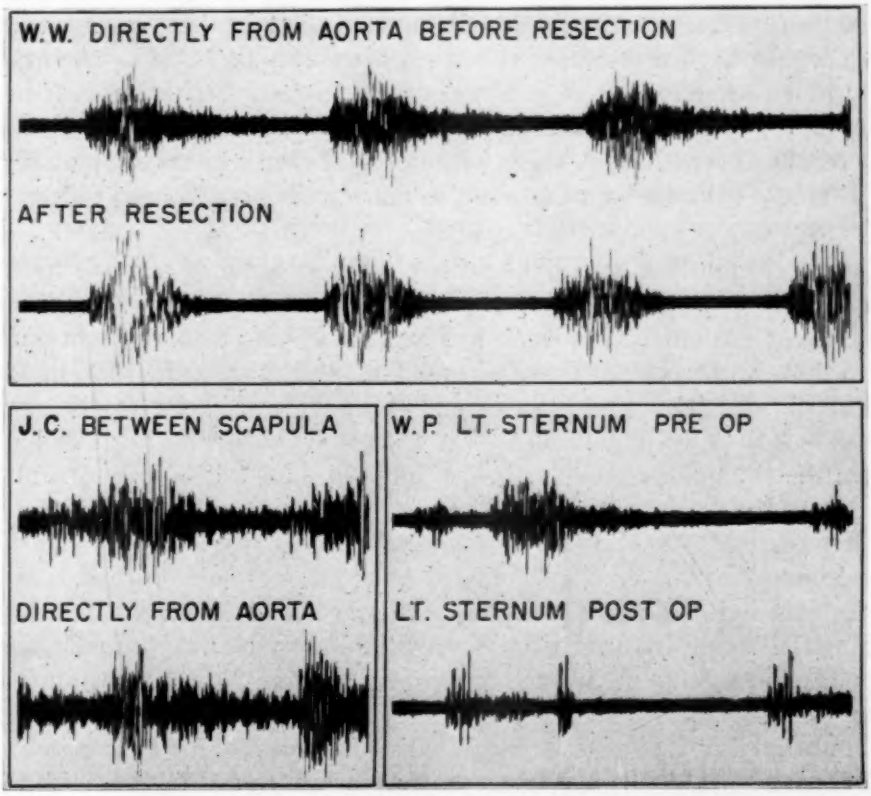

Fig. 3.—Continuous murmurs from coarctation of the aorta, demonstrating: their origin from the aorta and the influence of surgical improvement in degree of stenosis (W. W.); their transmission from the aorta to the back (J. C.); and their occasional presence on the precordium and disappearance after surgical repair (W. P.).

Auscultatory Findings on the Posterior Chest Wall.—Posteriorly, one hears a soft, blowing, late-systolic murmur between the scapulae, with the same characteristics as the typical systolic murmur described on the anterior chest wall. It frequently may be heard directly on dilated palpable arteries and be made to disappear with pressure of the stethoscope.

Careful auscultation over the fourth and fifth spinous processes reveals other important characteristics regarding timing, intensity, and pitch. Here the systolic murmur may extend far into diastole or be continuous throughout the entire heart cycle. A continuous murmur throughout the heart cycle was heard and recorded over the spine in Patients J.C., W.P., J.D.G., W.W., and L.N. The

continuous murmurs were best heard with the patient prone, pillow under the chest and the arms at the sides. Firm pressure with diaphragm stethoscope further augments the faint, high-pitched, continuous murmurs. These "long" or continuous murmurs—one hears the first sound followed by a high-pitched crescendo-decrescendo murmur—have been aptly termed "floating" by Dr. C. Glenn Sawyer.

Murmurs Heard Directly From the Aorta.—In 15 patients, auscultation was performed before resection in the operating room, with a sterile stethoscope or with the barium-titanate phonocatheter applied directly to the aorta below the stenosed segment. The results of this study are shown in Table I. An extremely loud murmur was present in all instances except in those 2 patients with complete obstruction. The point of maximal intensity is approximately 2 to 3 cm. below the stenosis and corresponds closely with the level of maximal poststenotic dilatation. Directly over the coarctation the murmur is loud but considerably less than below.

The aortic murmur varied according to the degree of stenosis as follows: (1) A continuous murmur, or one extending more than half way through diastole, was heard in 8 patients. It was always associated with a coarctation orifice less than 2.5 mm. in diameter. The converse (i.e., an orifice of 2.5 mm. or less was always accompanied by a murmur extending all or most of the way through diastole) was true with one exception. This exception was in the 8-week-old infant, in whom the collapsed specimen had an internal diameter of only 1 mm., while the murmur barely extended into diastole (Table I). Phonocardiography did prove it to extend past the second sound. In addition, this particular coarctation specimen was extremely elastic, so that the orifice stretched easily to a diameter of 4 mm. The pitch of the aortic continuous murmurs was high, approaching that heard from early aortic valvular regurgitation. Usually, a systolic component could be felt with the finger as a thrill. A fully continuous aortic murmur is illustrated in Fig. 3 (W.W.). (2) An orifice with an internal diameter of 3 mm. or greater was always associated with a systolic murmur *not* extending past the second sound. The shortest murmur arose from the aorta with the least stenosis (an oval orifice 6 to 8 mm., in J.B.). It began well after the first sound and ceased clearly before the second sound. In general, the systolic murmurs were lower in pitch and louder and coarser in quality than the continuous ones. (3) With complete obstruction, a very soft, late-systolic murmur was heard near the entrance of the intercostal collaterals (Fig. 2,*A*).

Murmurs from the Collateral Channels.—In this study there are three types of recordings from which definite conclusions can be drawn concerning the murmurs arising from turbulent collateral blood flow. All involve direct recordings over the vessels: (1) from the completely obstructed aorta where the collateral arteries empty, (2) from the surface of the surgically exposed collateral arteries, and (3) from the skin over superficial collateral vessels. On two separate occasions, conditions permitted testing of each of these three situations, and in no instance was a continuous murmur heard or recorded from a collateral channel. In many such instances a soft, late-systolic murmur was found as the "typical"

murmur of coarctation, as described previously. By no means, however, was a murmur always picked up from collateral channels even when they were greatly dilated. The left subclavian artery was surprisingly free of murmurs.

Esophageal and Tracheal Murmurs.—When the phonocatheter was passed into the esophagus under anesthesia in the operating room, or by having the patient swallow it in the laboratory, the aortic murmur was clearly detected and sharply localized. The esophageal murmur checked closely with directly recorded aortic murmurs on each of 4 patients. The esophageal murmur, therefore, was taken as representing the murmur of the coarctation itself. As the phonocatheter approached the coarctation from above, the murmur suddenly became audible, and quickly reached its maximal intensity. In conjunction with x-ray (Fig. 4) one may localize the exact level of the stenosis and aneurysm. This technique, of course, is equally efficient in evaluating the murmurs persisting after surgery. In one patient, P.R., the aortic murmur was clearly audible and recorded via the respiratory passages. A nasal stethoscope was constructed using two extra earpieces as "nose pieces." The patient was taught to hold his breath after a short inspiration, with the glottis open and the "nose pieces" applied to the nares.

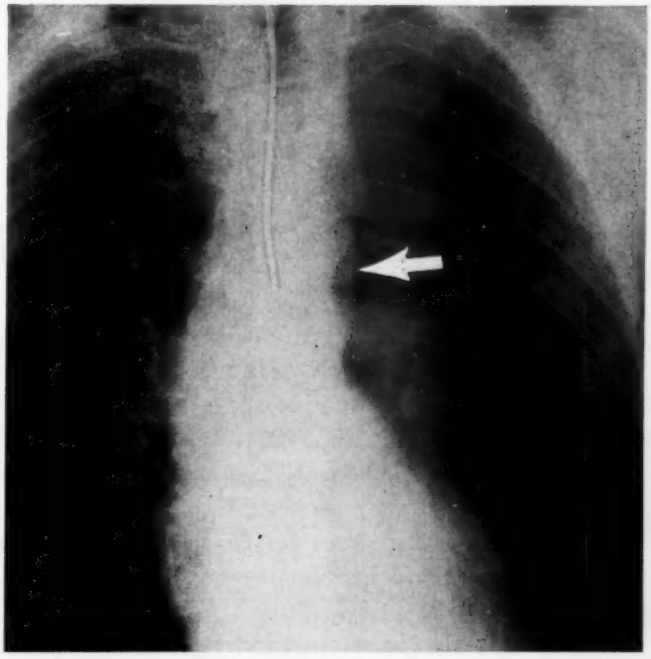

Fig. 4.—X-ray of Patient G. Mc., illustrating the esophageal phonocatheter technique. The tip of the phonocatheter is positioned by the intensity of the aortic murmur, and this site corresponds to the level of maximal poststenotic dilatation.

Murmurs Persisting After Resection.—Immediately after resection and end-to-end anastomosis, a murmur always persisted in the aorta below the suture line. It was short, systolic, and moderately loud. Postoperatively this murmur was well heard on the back between the scapulae and over the precordium. At

1-week follow-up examinations after surgery a systolic murmur persisted on the chest wall in all patients except P.R. In W.S. and G.Mc. the anterior diastolic "aortic regurgitation" murmur persisted, as described previously. No continuous or diastolic murmurs persisted on the back postoperatively.

Hemodynamic Source of the Aortic Murmurs.—The blood flow through the coarctation and the pressure in the aortic arch are illustrated for two extremes of stenosis by the tracings in Fig. 5. The pattern of the blood flowing through the coarctation matches closely the pattern of the pressure pulse in the aortic arch.

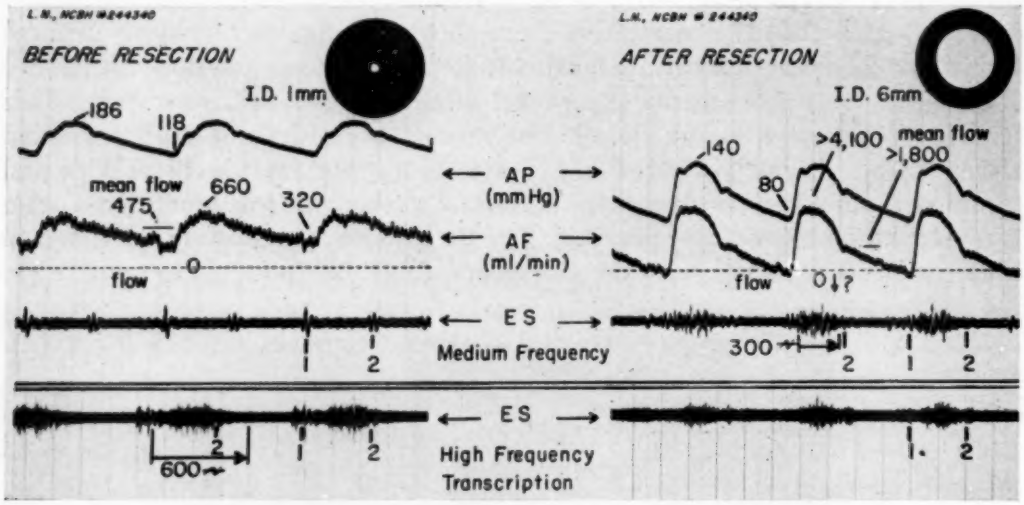

Fig. 5.—Changes in the aortic murmur, flow, and pressure resulting from surgical intervention in congenital coarctation of the aorta. *AP* is aortic pressure; *AF*, aortic flow; *ES*, esophageal sounds. The high-frequency transcription of the sounds was taken from a tape recording made before and after the resection.

Before resection, this flow through a 1-mm. orifice was but a fraction of the normal aortic flow. It is seen, however, that under this anatomic condition, this volume flow (660 to 320 c.c./min) gave rise to a long, smooth, high-frequency murmur of a crescendo-decrescendo shape, matching closely the flow pulse from which it arose. Resection and end-to-end anastomosis improved the internal cross section to an estimated diameter of 6 mm. and brought about a great improvement in blood flow. (The zero flow reference was not determined here because the necessary occlusion below the flowmeter endangered the arterial suture line.) This change in the anatomy toward normal caused the murmur to shorten. The persisting murmur was also lower in pitch, coarser in quality, and louder.

Relationship of Arterial Pressure to Stenosis.—The data of Table I shows the prevalence of hypertension in this series. It is notable that in the 3 patients with the least stenosis (between 8 to 5 mm. i.d.) only a systolic hypertension was present at the time of admission, and they were normotensive under resting hospital conditions.

B. *Experimental Coarctation.*—

The typical effect of a graded symmetrical constriction with a wire loop on a dog's aorta is illustrated in Fig. 6. During this procedure the mean arterial

pressure in the upper aorta remained relatively constant, probably through reflex mechanisms from the arch and carotid sinus. The normal i.d. of the aorta of this animal was calculated at 6.5 mm. and carried a normal flow pulse.[9] The earliest changes with increasing stenosis are seen best in the flow pulse contour. These early changes consist of a flattening of the pulsation, particularly at the peak systolic flow, and the abolition of the period of reverse flow at the time of incisura. They were apparent in spite of the failure of the constriction to reduce the mean flow until the calculated internal diameter became less than 3 mm.

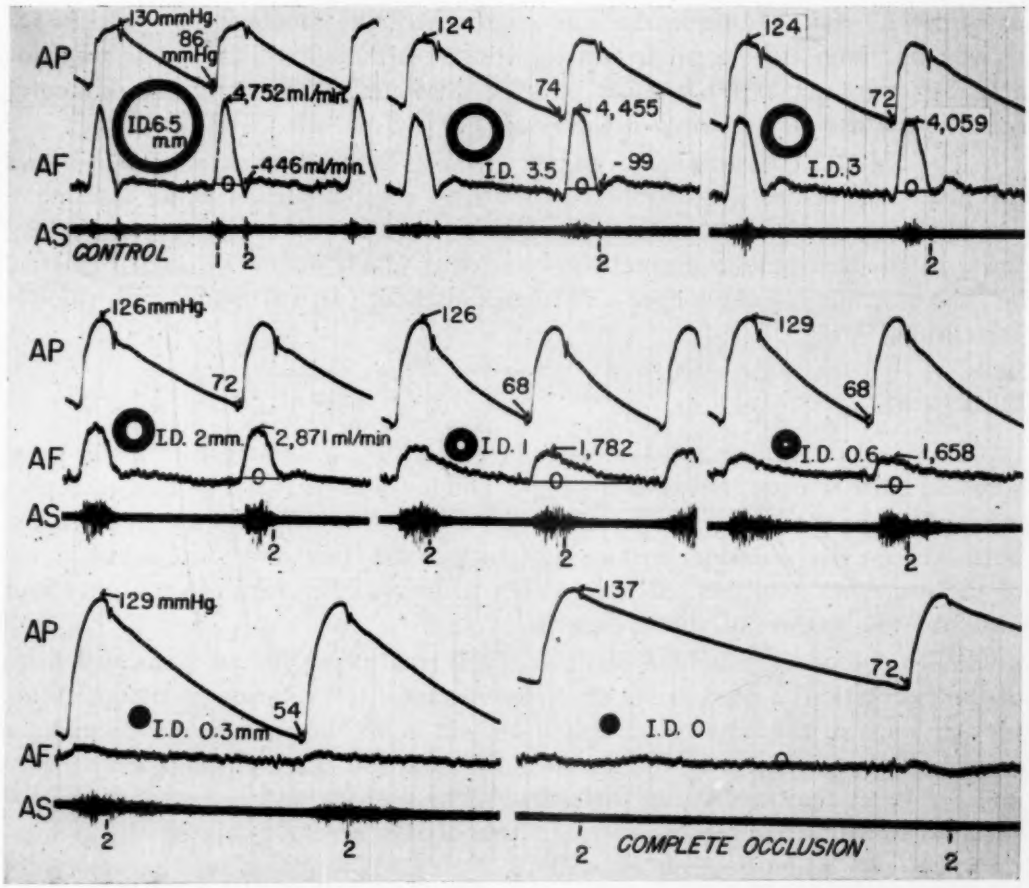

Fig. 6.—Experimental graded coarctation of a dog's aortic isthmus. *AP* is aortic pressure; *AF*, aortic flow; *AS*, aortic sounds through medium-frequency system. The second sound is labeled *2*.

During these early stages of constriction a systolic murmur, if not already present, began softly in mid-systole, gradually increased in duration, extending in both directions toward the first and second sounds, and increased in intensity and coarseness until the systolic interval was completely filled with murmur. In the experimental preparation the duration of the systolic murmur equaled that of the systolic interval when the internal diameter was reduced to 2 mm. At an internal diameter of 2 mm. the flow pulse was rounded during systole and flat during

diastole. The shape (or envelope) of the murmur fitted into this contour. It now had filled systole and had increased in intensity to obscure the heart sound. To the ear this had a coarse quality.

With further constriction taking us into the degree of stenosis seen most frequently in congenital coarctation, the flow pulse assumes a contour similar to the pressure pulse. This contour can be seen in the tracings taken at an internal diameter of 1 mm. With this increase in the early diastolic flow, the murmur extended into the diastolic period. As the orifice was further narrowed, mean flow was rapidly reduced, but the contour maintained the pressure pulse pattern. As complete occlusion was approached, the murmur decreased in intensity but increased in pitch and duration. Although this murmur was not actually continuous, it fell short only because under the acute experimental conditions the reflex slowing of the heart greatly extended diastole.

The Effect of Hypertension on the Stenosis-Murmur Relationship.—When the arterial pressure was doubled by infusing norepinephrine while keeping a constant degree of stenosis, the flow and turbulence patterns changed slightly toward those heard under normal tension with a slightly smaller internal diameter, i.e., the murmur became longer and higher pitched. It was louder with the hypertension.

DISCUSSION

The diagnosis of coarctation rests largely on (1) a difference in blood pressure and pulse strength between the upper and lower aorta, (2) a systolic murmur, especially over the left upper chest, and (3) evidence of collaterals, such as visible pulsations on the posterior chest and notching of the ribs. The more subtle study of the murmurs as presented here serves to predict the surgical anatomy and evaluate the success of the operation.

With the development of newer surgical treatments for mechanical defects of the circulation, a need arises for a more exact interpretation of the auscultatory findings in the physical examination. It is no longer sufficient to make a simple categoric diagnosis, for we need to know the exact pathologic anatomy and the functional severity of the lesion. The position and intensity of the associated murmur are insufficient. In this study, we have related the timing-duration and pitch-quality, as well as the position-intensity characteristics to the pathologic anatomy and the physiologic severity. In order to find the source of the murmurs, and to define their characteristics, we have recorded the vibrations directly from the artery wall at the time of surgical exposure, as well as the blood flow pattern through the distorted segment. Special nonsurgical techniques of nasal and esophageal auscultation were also employed to give pre- and postoperative data concerning the aorta.

Turbulence and Murmurs.—Murmurs arise from turbulent blood flow and vibration of the vascular structures. The physical conditions necessary for turbulence are abundantly present in uncomplicated coarctation of the aorta. There are two separate types of turbulent conditions: (1) those in the aorta below the stenosis, and (2) those in the collateral channels. In the aorta there is a high

blood velocity entering through a narrow orifice into a wide channel. Often there is a poststenotic dilatation of the aorta. In the collateral channels the increased blood flow exceeds that necessary for stable relationship between velocity and vessel diameter. Turbulence in both the collaterals and aorta is maximal during systole when blood velocity is maximal. It is continuous only under the special conditions of an aortic orifice less than 2.5 mm. i.d., when a high-velocity jet of blood flows throughout the cardiac cycle. The variations in blood viscosity and arterial pressure apparently do not greatly alter the important murmur characteristics.

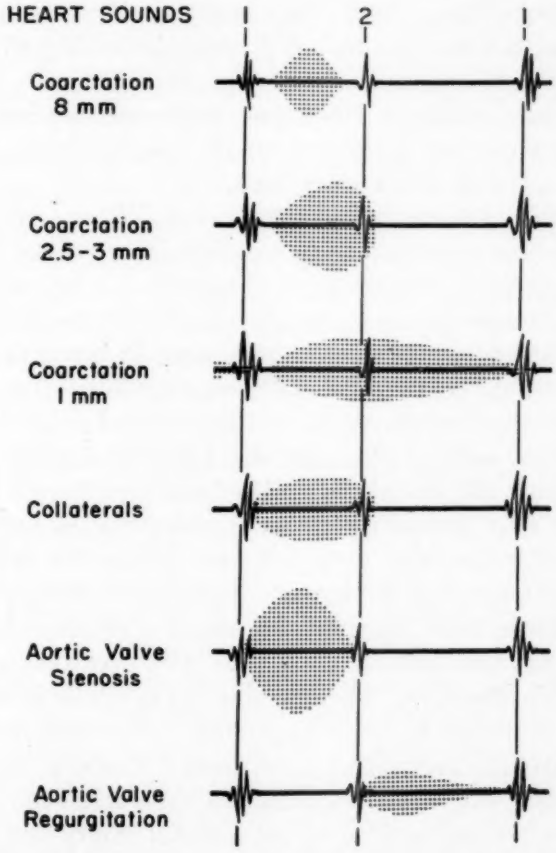

Fig. 7.—Diagrammatic survey of relative timing and intensity, according to their source, of murmurs commonly found in patients with coarctation.

Fig. 7 shows the murmurs associated with coarctation and gives their source. What one hears at a given point on the chest wall represents a summation of the collateral murmur and one of the three types of murmur due to aortic constriction. *When obstruction of the isthmus is complete*, a systolic murmur is heard over the interscapular spine, in the esophagus, or through the nares. The collaterals are well developed and display their soft, late-systolic murmur widely over the chest from the intercostals and internal mammaries, as well as over the supraclavicular vessels. *When the stenosis is minimal* (i.e., no more than to an internal diameter of 2.5 mm.), the loud, aortic systolic murmur is heard over the fourth and fifth

dorsal spines and from the esophagus and nares. The aortic murmur is also heard widely over the chest and resembles the collateral murmur. The collaterals are small and develop a weak murmur. *When the stenosis is near complete* (i.d. of 2.5 mm. or less), a continuous or nearly continuous murmur is heard in the esophagus and, often, over the back. This continuous murmur may be transmitted to the precordium and should be differentiated from aortic valvular regurgitation.

The diastolic murmur of aortic regurgitation may be differentiated from the diastolic component of the continuous murmur on the basis of location-transmission and pitch-quality. The systolic murmur of aortic valvular stenosis is very loud, often with a thrill in the aortic area, beginning without clear separation from the first sound and ending before the second sound. It, like the murmur of aortic regurgitation, persists after repair of the coarctation. The murmur of a patent ductus arteriosus was not encountered in this study, but would be expected to be loud over the pulmonary area.

The Relationship of the Coarctation to the Blood Flow and Arterial Pressure.—The primary objective of surgical intervention is to relieve the arterial hypertension in the upper parts of the body. There is no good reason or evidence to ascribe this hypertension to anything other than the mechanical obstruction of the aorta and its attendant increase in resistance to blood flow. With minimal degrees of obstruction the flow pulse contour deviates from normal,[9] but the mean flow through the aorta is not materially affected until the i.d. is reduced to approximately 50 per cent of the original. These beginning stages of increased resistance are apparently matched by the increased pressure difference across the coarctation. This increasing pressure difference is sufficient to maintain blood flow without measurable hypertension. When the coarctation reaches 5 and 8 mm. i.d., however, systolic hypertension only develops and is accentuated by exercise. In these early stages of increased resistance the systolic peak of the flow pulse is reduced and rounded off. The short mid-systolic murmur is an expression of this damping. The low-velocity diastolic backflow and resonant flow waves[9] are retained without murmurs. The collateral development is poor, and these patients may suffer permanent damage to the spinal cord while the aorta is clamped for repair. Protective measures such as hypothermia or pump bypass from the left atrium to the femoral artery are indicated in these instances. Orifice diameters between 5 and 3 mm. are critical, in that a small difference here results in a great change in blood flow, and a constant hypertension develops. Collateral development may be further judged at the time of surgery by pressure measurements in the lower arteries before and after clamping the aorta. All patients with a stenosis from 2.5 mm. i.d. to complete obstruction have serious impairment of flow through the isthmus and rely on the resultant hypertension and well-developed collaterals to supply the lower regions of the body. Surgical repair is highly indicated and protective measures for the spinal cord are not ordinarily needed if no more than two sets of intercostal collaterals are ligated for the repair procedure.

From the point of view presented here for the treatment of hypertension there appears to be little gained by providing an internal diameter of more than

8 mm. One patient, J.M., with an orifice of 4 by 7 mm. involving the orifice of the left subclavian artery, had a very thin-walled aneurysm. In such instances it may be advisable to use a graft. Grafting may not, therefore, be necessary if an i.d. of 8 mm. can be otherwise attained. The question of incidence of subacute bacterial endocarditis on operative sites providing less than a normal lumen can be answered only by long-term follow-up studies of patients with coarctation.

The Aortic Valve.—The aortic valve is said to be bicuspid in 40 per cent of the patients with coarctation. Therefore, when a diastolic decrescendo murmur is heard on the precordium, it is usually diagnosed as aortic valvular regurgitation and bicuspid valve. That such an interpretation may frequently be in error follows from three lines of evidence. (1) A precordial diastolic decrescendo murmur in patients with coarctation may actually originate from the site of coarctation in the thoracic descending aorta, as the diastolic component of a continuous murmur. In this series of patients, 1 out of 3 such precordial murmurs was proved to arise from the coarctation. (2) Although two murmurs typical of early aortic regurgitation were heard preoperatively, and persisted postoperatively, two murmurs also typical of aortic valvular stenosis were heard undiminished pre- and postoperatively. (3) Burch,[10] on theoretical grounds, points out that a bicuspid valve should display stenosis and not regurgitation. Autopsy has been performed on only one patient (D.L.) of this series, and a bicuspid valve was not reported, although both aortic and mitral stenosis were found along with endocardial fibroelastosis. At present, only long-term follow-up would seem to offer a complete answer to the functional manifestations of bicuspid valve.

SUMMARY AND CONCLUSIONS

From 20 consecutive patients treated surgically for coarctation of the aorta an interpretation is presented for the variations in systolic, diastolic, and continuous murmurs. The murmurs were recorded directly from the surface of the arteries and from the esophagus by means of a catheter-tip microphone, as well as from the chest wall and through the nasal airway with the Sanborn heart sound microphone. The abnormal blood flow pattern responsible for the aortic and collateral murmurs was recorded by means of the surgical probe of the square-wave magnetic flowmeter for unopened vessels. The aortic obstruction was measured as the internal diameter of the resected specimen and correlated with the aortic blood flow and murmurs. The basis for interpretation of the aortic murmur in stenosis correlations was established in 25 dogs by producing graded stenosis with a wire loop about the isthmal aorta and recording the aortic murmur, flow, and pressure.

The following conclusions were reached: (1) There are two separate sources of murmurs in uncomplicated coarctation of the aorta; these are (a) from the widely distributed collateral channels, and (b) from the aorta below the coarctation itself. (2) From the collateral channels a systolic murmur only arises. It begins in early systole, clearly separated from the first sound, and builds up in loudness into, and ends in, the second sound. (3) The murmur in the poststenotic aorta may be accurately recorded from the esophagus or directly

from the aortic wall with a catheter-tip microphone; it may usually be heard on the posterior and anterior chest wall. The barium-titanate phonocatheter is extremely useful in evaluating murmurs directly from the heart and vessels during surgery. (4) The degree of aortic stenosis present in a given patient may be predicted from the duration, intensity and general pitch of the murmur present in the aorta below the coarctation. (5) Coarctation with an internal diameter of 3 mm. or greater is accompanied by an aortic systolic murmur not extending beyond the second sound. It is coarse and of blowing quality. (6) Complete obstruction of the aorta is attended by strong collateral systolic murmurs but no significant aortic murmurs. (7) A continuous murmur heard from the aorta, esophagus, or over the spine between the scapulae, means that the coarctation orifice is patent to no greater than 2.5 mm. in diameter. (8) The diastolic component of the continuous murmur transmitted to the precordium may lead to a mistaken diagnosis of aortic regurgitation. The diastolic decrescendo murmur of aortic regurgitation is commonly found in patients with coarctation (10 per cent of the present series), but is not transmitted to the back. It further differs from the continuous murmur of coarctation by its unique pitch and quality. (9) Aortic valvular stenosis is also commonly coexistent with coarctation (10 per cent of the present series). Its murmur differs from the aortic systolic murmur and the collaterals' murmur of coarctation by beginning without separation from the first sound and ending before the second sound. (10) The mean aortic flow through the isthmus is not reduced unless the diameter of the lumen is compromised more than 8 mm. There is little to be gained hemodynamically by surgical provision of an internal diameter greater than 8 mm. One good indication for surgical intervention for orifices of 4 to 8 mm. is provided by the possibility of serious poststenotic aneurysm. Because of poor collaterals in the group with orifices of 3 to 8 mm. the surgeon may anticipate the need for measures protective to the spinal cord and kidneys during the aortic clamping necessary to perform the repair. (11) Postoperative evaluation is improved by the interpretations of murmurs provided by this study.

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A Different Concept of Prothrombin Time Control for Anticoagulative Therapy

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The early investigations of Link[4] established that the administration of oral anticoagulants produces hypocoagulability or hemorrhage, depending on the amount of anticoagulant administered. To control thrombosis, but avoid bleeding, the dosage needs to be carefully regulated. The assay procedures used to regulate the dosage have received much attention. The two-stage prothrombin determination advocated by Seegers[9] and by Olwin[7] measures only prothrombin accurately. Contrary to the opinion of Biggs and Macfarlane,[1] prothrombin is reduced below 50 units per milliliter by the administration of the anticoagulant in the dosages used in this country. However, the two-stage prothrombin determination is not influenced by the other known factors which the anticoagulants reduce. The one-stage prothrombin time is less specific. Therefore, it is affected by more components of the blood coagulation mechanisms, which are reduced during administration of the oral anticoagulant. Link[5] evaluated these two methods and pointed out the practical advantages of the Quick one-stage method for routine use.

A further modification of the one-stage prothrombin time by Ware and Stragnell[11] renders this test more sensitive; however, it also complicates the test. The Quick one-stage technique is used in this laboratory[8] to guide the administration of oral anticoagulants. The one-stage prothrombin time is influenced by concentrations of plasma prothrombin, autoprothrombin I (factor VII), ac-globulin (labile factor), and fibrinogen. Most anticoagulant drugs at least reduce prothrombin, autoprothrombin I, and autoprothrombin II (PTC or Christmas factor),[3] but have not been shown to affect the physiologic levels of ac-globulin and fibrinogen. Therefore, the one-stage measures the known factors reduced by anticoagulative therapy, with the exception of autoprothrombin II.

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TABLE I. PROTHROMBIN TIME RESULTS USING THREE DIFFERENT THROMBOPLASTINS

#1	#2	#3
13^{1}	12^{1}	15^{1}
14^{19}	12^{2}	15^{1} 16^{4} 17^{13} 19^{1}
15^{23}	12^{6} 13^{2}	16^{4} 17^{14} 18^{4} 19^{1}
16^{22}	12^{1} 13^{1} 14^{1} 16^{1}	16^{2} 17^{4} 18^{9} 19^{3} 20^{2} 21^{2}
17^{16}	14^{2} 16^{2}	16^{1} 17^{1} 18^{1} 19^{8} 20^{3} 22^{1} 23^{1}
18^{19}	13^{2} 14^{3} 15^{3}	16^{1} 17^{4} 18^{3} 19^{2} 20^{4} 21^{1} 23^{1} 25^{1} 26^{1} 28^{1}
19^{21}	14^{2} 15^{3} 16^{3} 17^{1} 18^{1} 19^{1}	18^{1} 19^{4} 20^{4} 21^{3} 22^{5} 23^{1} 24^{1} 25^{1} 30^{1}
20^{29}	14^{1} 15^{2} 16^{4} 17^{2} 18^{2} 19^{2}	19^{2} 20^{3} 21^{4} 22^{4} 23^{4} 24^{6} 25^{3} 26^{2} 27^{1}
21^{28}	15^{1} 16^{1} 18^{4} 20^{1}	18^{1} 20^{1} 22^{5} 23^{4} 24^{4} 25^{5} 26^{4} 27^{2} 28^{1} 29^{1}
22^{22}	14^{1} 17^{1} 18^{4} 19^{3} 20^{2}	21^{2} 22^{2} 23^{3} 24^{4} 25^{5} 26^{2} 28^{1} 29^{1} 30^{1} 32^{1}
23^{23}	15^{1} 17^{1} 18^{3} 19^{2} 21^{1}	21^{2} 22^{2} 24^{4} 25^{2} 26^{5} 28^{2} 29^{3} 30^{3}
24^{30}	19^{2} 20^{3} 21^{1}	21^{1} 22^{1} 23^{1} 24^{1} 25^{1} 26^{4} 27^{4} 28^{4} 29^{1} 30^{3} 31^{2} 33^{2} 34^{3} 35^{1} 37^{1}
25^{33}	19^{1} 20^{2} 21^{4} 22^{3} 24^{1}	24^{1} 25^{1} 26^{2} 27^{2} 28^{3} 29^{3} 30^{3} 31^{5} 32^{4} 33^{1} 35^{1} 36^{2} 37^{1} 40^{1}
26^{22}	19^{2} 22^{1} 23^{1} 24^{1} 28^{1}	25^{1} 26^{1} 27^{1} 29^{3} 30^{2} 31^{1} 32^{1} 33^{2} 34^{3} 36^{2} 37^{2} 39^{1}
27^{29}	20^{1} 23^{1} 25^{1}	29^{2} 30^{2} 32^{3} 33^{1} 34^{5} 35^{5} 37^{2} 38^{5} 39^{2} 43^{1} 46^{1}
28^{28}	19^{1} 20^{1} 21^{1} 23^{2}	29^{2} 30^{1} 32^{2} 33^{2} 35^{1} 36^{1} 37^{1} 38^{1} 39^{1} 41^{2} 43^{2} 44^{2} 45^{2} 46^{2} 47^{1} 48^{2} 50^{1} 57^{1} 75^{1}
29^{14}	22^{1} 25^{1}	30^{1} 32^{1} 34^{1} 35^{1} 36^{4} 39^{1} 40^{1} 41^{1} 42^{3}
30^{22}	22^{1} 23^{3} 25^{1} 26^{1}	30^{2} 31^{1} 32^{2} 34^{1} 35^{1} 37^{2} 39^{1} 40^{1} 41^{1} 42^{3} 43^{2} 45^{1} 47^{1} 48^{1} 49^{1} 62^{1}
31^{14}	21^{1} 28^{2}	31^{1} 36^{1} 39^{1} 40^{1} 43^{3} 45^{1} 48^{1} 50^{3} 51^{1} 65^{1}
32^{10}	27^{1}	35^{1} 43^{2} 45^{1} 47^{2} 48^{1} 52^{1} 54^{1} 73^{1}
33^{10}	25^{2}	41^{1} 42^{1} 43^{1} 48^{1} 52^{2} 53^{2} 54^{1} 56^{1}
34^{8}	27^{1} 29^{1} 31^{1}	35^{1} 36^{1} 47^{1} 50^{1} 53^{1} 55^{2} 58^{1}
35^{5}		49^{1} 55^{2} 57^{1} 60^{1} 63^{1} 64^{1} 80^{1}
36^{2}		55^{2}
37^{6}	32^{1} 36^{1}	42^{1} 56^{1} 57^{1} 67^{2} 89^{1}
38^{1}		80^{1}
39^{7}	31^{1} 34^{2}	49^{1} 50^{1} 51^{1} 52^{1} 65^{1} 80^{1} 90^{1}
40^{4}	28^{1}	30^{1} 43^{1} 57^{1} 85^{1}
41		
42^{1}		80^{1}
43^{1}		90^{1}
44^{2}	34^{2}	48^{1} 55^{1}
45^{1}		63^{1} 65^{1} 94^{1} 140^{1}
46^{1}		55^{1}
47		
48^{2}		74^{1} 110^{1}
49		
50^{1}		78^{1}
51^{3}	40^{1}	63^{1} 71^{1} 88^{1}
486— Total		

The sensitive reagent in the one-stage prothrombin test is thromboplastin, which is obtained from animal tissue but is not a well-defined substance. Some factors are known to be present in thromboplastin which are also constituents of normal plasma and take part in clotting. These substances could very well mask a corresponding deficiency in plasma. This may account for the fact that some thromboplastins give consistently shorter prothrombin time values than others, constituting a thromboplastin less sensitive to changes in plasma. This possibility was recognized by Mann and Hurn,[6] in 1950.

A less sensitive thromboplastin could indicate that a patient is stable and well regulated, two characteristics in which the physician is interested. The less sensitive thromboplastin would give the physician a false sense of security. A thromboplastin more sensitive to changes in the plasma would offer more information.

MATERIAL AND METHODS

Thromboplastins.—(1) Difco Bacto-thromboplastin is prepared according to specifications of the company. (2) Simplastin, a desiccated product, containing both thromboplastin and calcium, is reconstituted by adding distilled water. (3) Acuplastin, also a desiccated product, containing calcium as well as thromboplastin, is reconstituted by adding distilled water.

The other materials employed are 0.1 molar sodium oxalate and 0.025 molar calcium chloride.

Methods.—4.5 ml. of blood carefully drawn is well mixed immediately with 0.5 ml. of 0.1 molar sodium oxalate, and then centrifuged to obtain plasma. When #1 thromboplastin is used, 0.1 ml. is added to each of several small tubes, which also contain 0.1 ml. of 0.025 calcium chloride. When either of the other two thromboplastins, #2 or #3, are used, 0.2 ml. is added to small tubes. From this point the technique of performing the test is the same. The tubes containing thromboplastin and calcium are placed in a water bath of 37°C. and allowed to warm up to 37°C. Then, 0.1 ml. of plasma is forcefully blown into the tube and a stop watch started simultaneously. The first appearance of a clot is the end point.

RESULTS

Over a period of several months a large number of patients were followed using these three thromboplastins. These patients were receiving anticoagulant drugs, but neither the type of drug nor the dosage given was considered. The patients were chosen at random.

Table I represents a comparison of the three thromboplastins. Number 1 thromboplastin was used as the base, and the times obtained on the same blood with the other two thromboplastins were recorded. The superscript represents the number of different bloods which gave that result.

Routinely, duplicate prothrombin times are done on each plasma and must agree within 3 per cent before the results can be recorded. For example, a value of 30 seconds would indicate the results must be duplicated within 1 second. A value recorded as 60 seconds must be duplicated within 2 seconds.

Thromboplastin #2 resulted in prothrombin times which were usually shorter than those of thromboplastin #1. Thromboplastin #3 gave prothrombin times which were always more prolonged, and several in each group which were completely out of range. For example, the 28 values of 28 seconds using thromboplastin #1 gave values of 19 to 23 seconds with thromboplastin #2, while with

thromboplastin #3 these same 28 values ranged from 29 to 48 seconds, with one prothrombin time of 50, another of 57, and another of 75 seconds. No correlation was found between these long values and the particular drugs given.

DISCUSSION

A careful consideration of these results indicates that a plasma which gives a long prothrombin time when tested by #3 thromboplastin is different from another plasma which gives a short prothrombin time when the same thromboplastin is used. This difference, however, is not so readily apparent when either #1 or #2 thromboplastin is used. This difference is important to the physician regulating a patient and should be known. There are several factors to consider in evaluating this long prothrombin time. Possibly, the patient is more sensitive to the drug; he is a potential bleeder; or he is lacking in some factor which is present as an impurity in the less sensitive thromboplastins.

In following a group of patients over a period of time it was discovered that the same patients had consistently longer prothrombin times with #3 thromboplastin than with the other two. This, although not conclusive, is certainly good evidence that the plasma giving much longer times with #3 thromboplastin in comparison with #1 and #2 is different. This difference could only be picked up using #3.

Autoprothrombin I (factor VII) has been shown to be one of the clotting factors reduced during anticoagulative therapy.[10] It has also been shown that some thromboplastins contain autoprothrombin I. This fact leads to the speculation that these differences in results obtained using thromboplastins #1, #2, and #3 could be a result of less autoprothrombin I being present in thromboplastin #3. The prothrombin times which are so much longer with #3 than with #1 and #2 thromboplastins suggest that the plasmas have a very low, or absent, autoprothrombin I. However, we know from our assay procedures that autoprothrombin I levels are very low in all patients receiving therapy.[2]

Another problem introduced by the variability of these thromboplastins which might be worth mentioning involves the patient's changing of laboratories. The table of comparisons can be useful to a doctor faced with this situation.

SUMMARY

Three different thromboplastins were used in the Quick one-stage prothrombin time on plasmas of patients to whom oral anticoagulants had been administered. Thromboplastin #1 gave very uniform results. Thromboplastin #2 gave shorter prothrombin times, and thromboplastin #3 gave more prolonged values and separated out a few plasmas which appeared to be different from the others.

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The Racial Incidence of Heart Disease at Groote Schuur Hospital, Cape Town. Part II. Hypertension and Valvular Disease of the Heart

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In a previous communication[1] the extremely low incidence of coronary vascular disease in the Bantu was described. In Whites, on the other hand, the disease is very common, whereas in the Cape Colored the incidence lies between that of the two other races. The Whites are mainly descendants of immigrants from Great Britain and the continent of Europe and are economically privileged. The Bantu occupy the lowest place in the socioeconomic scale, providing the unskilled and heavy labor, and are the descendants of immigrants from central Africa. They are a relatively unstable population. The Cape Colored originate from an admixture of European, Hottentot, and Malay stock and occupy a place in the socioeconomic scale midway between the Whites and the Bantu. All three races have the same geographic and climatic environment, but the socioeconomic and genetic differences are vast.

Groote Schuur Hospital was the main hospital serving the population of Cape Town and the surrounding districts during the five years under review, namely 1952 to 1956. It is an 854-bed hospital, with slightly more White beds than Non-White ones, and serves as the main teaching hospital of the Faculty of Medicine of the University of Cape Town. During 1955 and 1956, however, the 44 teaching beds of the New Somerset Hospital, which serves the Non-White population only, was included in this study, thus making the White and Non-White bed state approximately equal.

It is the purpose of this study to report the relative incidence of hypertension and valvular disease of the heart as obtained from electrocardiographic data in the three racial groups. Since a means test prevents the attendance of the wealthier section of the general population, the hospital population is selected. This scarcely affects the Non-Whites, but results in the partial exclusion of the wealthier Whites. The figures obtained in this survey are, therefore, a more accurate reflection of the Cape Colored and Bantu than of the Whites.

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MATERIAL AND METHODS

The material and methods have been described in detail elsewhere.[1-4] In brief, all inpatients and outpatients attending Groote Schuur Hospital and the 44 teaching beds of the New Somerset Hospital are included in the electrocardiographic service of the Cardiac Clinic. Over 99 per cent of the 21,582 records were interpreted by the author, so that any errors in electrocardiographic interpretation were constant in all racial groups. The same physicians and surgeons see patients of all races, and equal facilities for obtaining electrocardiographic investigation are available for all groups. The majority of inpatient electrocardiograms came from the medical wards, and almost all outpatient records came from the Medical Out-Patients Department. In all cases electrocardiograms consisted of the six limb leads and seven precordial leads, V_1-V_7.

The White and Cape Colored populations are a relatively stable group, whereas probably half of the Bantu are migrant male laborers between the ages of 20 and 40 years. Official estimated figures compiled by the Bureau of Census and Statistics, Pretoria, in 1951 and 1957, show the following figures: Whites—247,442 and 280,000, respectively; Cape Colored—272,314 and 351,100, respectively; and Bantu—49,793 and 67,800, respectively. The breakdown by decades of the three racial groups in 1951 is shown in Table I. The Bantu population is almost certainly underestimated.

TABLE I. AGE DISTRIBUTION OF POPULATION OF METROPOLITAN CAPE TOWN, 1951

DECADE	WHITES	CAPE COLORED	BANTU
10–19	39,169	63,801	Unknown
20–29	40,897	49,133	15,317
30–39	36,932	31,913	12,669
40–49	34,262	24,137	5,959
50–59	22,966	13,484	2,105
60–69	15,326	7,776	588
70+	11,780	4,297	249

The attendance of White and Cape Colored outpatients is approximately equal, and the inpatient admissions are also approximately equal (Reference 1, Table I). The Bantu subjects, although significantly fewer in number than either of the other two groups, were, generally, well represented in the hospital population; however, the older group were less well represented.[2]

A. HYPERTENSION

The electrocardiographic material was analyzed as follows: All patients were included in whom one or more casual blood pressure readings showed a diastolic pressure of at least 100 mm. Hg, irrespective of the systolic pressure (all pressures being expressed to the nearest 5 mm.). In a minority of patients the diastolic pressure was 90 to 95 mm. Hg, with a systolic pressure of 170 mm. Hg or over.

In the second group all patients who had electrocardiograms recorded solely for hypertension or hypertensive heart disease were studied. Analyses were made on electrocardiographic changes and on the height of the diastolic pressure. For practical purposes this meant excluding patients with coronary heart disease (482 Whites and 189 Cape Colored), because the electrocardiographic patterns were so much altered by this disease that the degree of hypertensive change could not be graded. Although this also meant that a certain number of patients with an elevated diastolic pressure was excluded, there was no particular racial association between hypertension and coronary disease. The percentage of Cape Colored patients with coronary heart disease and hypertension was only slightly greater than that of the Whites. Electrocardiographic patterns were graded into three degrees of severity. The first consisted of normal patterns. The second was slightly abnormal, showing left auricular hypertrophy or slight S-T-segment or voltage change. Auricular fibrillation without QRS-T change was also included. For left auricular hypertrophy the following

criteria were used: a P wave more than 3 mm. in height in any lead or more than 0.1 second in duration or when bifid, more than 0.04 second between peaks.[5] The criteria of Sokolow and Lyon[6] for voltage changes were used, namely, the sum of the left ventricular potentials (R wave in Leads V_5 or V_6 and S wave in Lead V_1) totals 35 mm. or more; the voltage of R in the precordial Lead V_5 or V_6 exceeds 26 mm.; the voltage of the R wave in Lead aV_L in the horizontal heart exceeds 11 mm.; or the R wave in Lead aV_F in the vertical heart exceeds 20 mm. S-T-segment abnormality consisted of minor depression without T-wave inversion, or U-wave inversion alone. Where T-wave inversion, marked S-T-segment depression, or prolongation of the intrinsicoid deflection over the left ventricle of more than 0.055 second, was present, the records were put into the third group. Included here also were intraventricular disturbances of conduction and nonspecific abnormalities.

Blood pressures were graded into four groups. The first group consisted of cases in which the diastolic pressure was 110 mm. Hg or less; the second, of cases in which the pressure was over 110 and up to 130 mm. Hg; the third, of cases in which the pressures were over 130 and up to 150 mm. Hg; and the fourth, of cases in which the diastolic pressures were over 150 mm. Hg.

B. VALVULAR DISEASE OF THE HEART

1. *Rheumatic Heart Disease and Rheumatic Fever.*—The diagnosis of rheumatic heart disease is almost always made on the basis of cardiac murmurs, systolic or diastolic in time, usually arising in the mitral valves. In the case of systolic murmurs it is recognized that difficulty may be experienced in differentiating the murmurs of aortic stenosis from those of arteriosclerosis, and those of mitral incompetence from functional and congenital murmurs. Diastolic murmurs, on the other hand, usually indicate rheumatic heart disease, with the exception of lone aortic valvular involvement. By far the majority of patients had mitral valvular involvement, alone or in combination with other valvular lesions, and diastolic murmurs were very frequent.

Bacterial endocarditis was included in rheumatic heart disease, but in the presence of severe hypertension, aortic incompetence was not necessarily regarded as valvular disease. However, admitting the occasional errors in diagnosis, whenever the clinical diagnosis was one of rheumatic valvular disease, it was accepted as such, since these errors would be consistent in all races. Rheumatic fever was diagnosed on the basis of the usual criteria of polyarthritis, chorea, or some other well-recognized manifestation of the disease, these being no different in Cape Town than elsewhere.

Almost all cases were referred to the Cardiac Clinic, where the question of congenital heart disease arises and where electrocardiographic investigation is performed. These cases have been excluded from this analysis whenever the diagnosis was made.

2. *Syphilitic Valve Disease and Aortic Aneurysm.*—In the presence of pure aortic incompetence, the differentiation of syphilitic from rheumatic disease may be difficult, and, occasionally, syphilis produces all the signs usually associated with stenosis and incompetence,[7,8] thereby increasing the difficulty of diagnosis. Hence, aortic incompetence has been analyzed separately. Those cases in which the clinical bias strongly favored rheumatic valvular disease have been regarded as such; those cases in which it favored syphilis, and in which aneurysm of the ascending or arch of the aorta has occurred (with or without aortic valvular involvement), have been regarded as syphilis; but those cases in which either diagnosis could be correct have been regarded as unknown. Because positive serologic reactions for syphilis occur so frequently in the Cape Colored and Bantu[9] without cardiovascular disease, these tests could not be relied upon in differential diagnosis.

Electrocardiographic analysis was of no value in the assessment of valvular disease of the heart. Many cases with established valvular disease have normal patterns, and when the tracing is abnormal, it reflects the particular heart chamber that is involved and not the disease process itself. It was occasionally of value in differentiating an organic systolic murmur from an innocent one, but usually this indicated a congenital and not a rheumatic lesion. However, the racial analysis is of value, because almost all patients with valvular heart disease or rheumatic fever are referred for electrocardiographic investigation, irrespective of their age, sex, or color, and certainly no racial selection is made.

RESULTS

During the five-year period, 1952 to 1956, the number of electrocardiograms requested for individual adults (over the age of 12 years) was 12,512. Although many patients had records taken repeatedly over the years in this analysis, each patient appears only once. The ratio of White to Cape Colored and Bantu (Table II) was 9.2:5.7:1. If patients over the age of 30 years were considered, the ratio was essentially the same (10:5.6:1) (10,478 patients).

TABLE II. RACIAL INCIDENCE OF ELEVATED BLOOD PRESSURE AND "HYPERTENSION"

RACE	RACIAL DISTRIBUTION OF ECGS		RACIAL DISTRIBUTION OF AN ELEVATED B.P.		RACIAL DISTRIBUTION OF HYPERTENSIVE ECGS	
	NUMBER	PER CENT OF TOTAL	NUMBER	PER CENT OF TOTAL	NUMBER	PER CENT OF TOTAL
White	7,232	58	2,495	57	1,738	54
Colored	4,497	36	1,716	39	1,325	41
Bantu	783	6	185	4	163	5
Total	12,512		4,396		3,226	

Hypertension.—The incidence of high blood pressure in the 12,512 patients in whom electrocardiograms were recorded is approximately 33 per cent, as shown in Table II. Of these 4,396 patients with an elevated blood pressure, 2,495 (57 per cent) were Whites, 1,716 (39 per cent) were Cape Colored, and 185 (4 per cent) were Bantu. After excluding the patients with an elevated pressure complicating other forms of cardiac disease (principally coronary vascular disease), there were 3,226 patients with hypertension or hypertensive heart disease, of whom 1,738 (54 per cent) were Whites, 1,325 (41 per cent) were Cape Colored, and 163 (5 per cent) were Bantu. The incidence of an elevated blood pressure and of hypertension, therefore, appears to be high in all three races. However, statistical analysis of these and subsequent data has not been possible because an absolute knowledge of the population from which the hospital subjects have been drawn is not available. That hypertension occurs commonly in all three racial groups appears to be a valid conclusion, and that there is little racial difference in incidence is probably correct.

The severity of hypertension in the three racial groups is shown in Tables III and IV. Using the electrocardiographic criteria described under *Material and Methods*, 41 per cent of the Whites had normal graphs, whereas only 35 per cent of the Cape Colored and 23 per cent of the Bantu had such patterns. On the other hand, 46 per cent of the Cape Colored and 55 per cent of the Bantu had tracings showing the greatest abnormality, as compared with 34 per cent of the Whites. This would suggest that hypertension is more severe in the Cape Colored and Bantu than in the Whites.

When hypertension was graded according to the height of the diastolic pressure, the difference was even more striking. Thus, 62 per cent of the Whites

had a diastolic pressure of 110 mm. Hg or less, whereas only 46 per cent of the Cape Colored and 48 per cent of the Bantu had pressures of this order. With diastolic pressures of 135 mm. Hg and over, the reverse was found, namely, that 23 per cent of the Cape Colored and 25 per cent of the Bantu, and only 12 per cent of the Whites, had pressures of this order.

It is possible that the presence of coronary vascular disease in the Whites is, in part, responsible for the apparent increase in severity of hypertension amongst the Non-White races. Coronary disease is so much more common in the Whites than in the Non-White races, and there is a frequent association with hypertension. In fact, the level of the hypertension may be affected by the presence of coronary disease. Therefore, the severity of the disease may be shown in the coronary system in the Whites more than in the rest of the cardiovascular system. The difference is certainly not due to selection of material, because equal numbers of White and Cape Colored patients are seen,[1] even though electrocardiograms are recorded more often in Whites (Table II).

The age and sex distribution of the patients with elevated blood pressure and hypertension is shown in Table V and Figs. 1 to 3. "Elevated B.P." refers to the total number of patients submitted to electrocardiography in whom an

TABLE III. THE SEVERITY OF HYPERTENSION AS ASSESSED ELECTROCARDIOGRAPHICALLY IN THE THREE RACIAL GROUPS

ECG GRADE OF SEVERITY	WHITES			CAPE COLORED			BANTU		
	MALE	FEMALE	PER CENT	MALE	FEMALE	PER CENT	MALE	FEMALE	PER CENT
Normal	310	399	41	179	284	35	17	22	23
Grade 1	175	257	25	96	158	19	18	19	22
Grade 2	272	325	34	228	380	46	57	30	55
Total	757	981	100	503	822	100	92	71	100
	1,738			1,325			163		

TABLE IV. THE SEVERITY OF HYPERTENSION AS ASSESSED ON THE BASIS OF DIASTOLIC PRESSURES IN THE THREE RACIAL GROUPS

BLOOD PRESSURE (MM. HG)	WHITES			CAPE COLORED			BANTU		
	MALE	FEMALE	PER CENT OF TOTAL	MALE	FEMALE	PER CENT OF TOTAL	MALE	FEMALE	PER CENT OF TOTAL
110 or less	485	597	62	268	345	46	53	26	48
115–130	182	272	26	137	269	31	23	21	27
135–150	62	73	8	68	135	15	12	15	17
Over 150	28	39	4	30	73	8	4	9	8
Total	757	981	100	503	822	100	92	71	100
	1,738			1,325			163		

elevated blood pressure was found. "Hypertension" refers to the selected group of patients having an elevated blood pressure after coronary vascular disease and other major cardiovascular diseases had been excluded.

Females outnumber males in both the White and Cape Colored groups—after the age of 50 in the former and after the age of 30 in the latter. The increased incidence in White and Cape Colored females cannot be attributed solely to a difference in attendance of the two sexes at the hospital. Excluding the gynecology department (from which very few electrocardiograms are requested) there are more male than female hospital beds, and, consequently, the annual admission rate of males is slightly higher than that of females. The annual female attendance at the Medical Out-Patients Department (the source of almost all outpatient electrocardiographic requests) is slightly greater than male attendance, so that the over-all attendance of both sexes is approximately equal. Electrocardiograms were performed on 3,792 White males, 3,440 White females, 2,109 Cape Colored males, and 2,388 Cape Colored females, so that electrocardiogram selection cannot account for the sex difference in incidence of hypertension. In the Bantu, however, the situation is completely different. Bantu males far outnumber the females in the local Bantu population,[1,2] and this is reflected by the attendance of the two sexes at the hospital. Approximately one third as many males as females attend the Medical Out-Patient Department and are admitted to the wards (excluding the gynecology wards). Five hundred and fourteen electrocardiograms were recorded on Bantu males and 269 on Bantu females. Moreover, the age distribution of the Bantu (Table I) shows a rapid decline in numbers after the age of 50, as compared with that of the Whites and Cape Colored. It is not surprising, therefore, that more hypertensive male than female Bantu are found.

When the data obtained from patients with an elevated blood pressure is analyzed (Table V and Fig. 1), the following conclusions can be drawn. The

TABLE V. SEX AND AGE OF PATIENTS WITH ELEVATED BLOOD PRESSURE AND HYPERTENSION IN THE THREE RACIAL GROUPS

	DECADE	WHITES		CAPE COLORED		BANTU	
		MALE	FEMALE	MALE	FEMALE	MALE	FEMALE
Elevated B.P.	10–19	5	11	9	8	2	1
Hypertension		5	11	6	6	1	—
Elevated B.P.	20–29	25	17	31	31	9	3
Hypertension		25	15	24	30	9	3
Elevated B.P.	30–39	71	51	60	99	16	16
Hypertension		55	41	45	98	15	13
Elevated B.P.	40–49	208	187	153	256	26	20
Hypertension		136	173	103	224	16	20
Elevated B.P.	50–59	328	362	224	300	29	24
Hypertension		165	269	162	254	29	24
Elevated B.P.	60–69	322	381	137	179	17	10
Hypertension		176	286	102	151	17	10
Elevated B.P.	70+	243	283	149	73	9	3
Hypertension		194	186	57	56	8	2

incidence of an elevated blood pressure is somewhat more common in the White female than in the White male after the age of 50, whereas the Cape Colored female far outstrips the Cape Colored male, and this commences two decades earlier. The peak incidence of hypertension also occurs in the Cape Colored female at least a decade earlier than in the rest of the population.

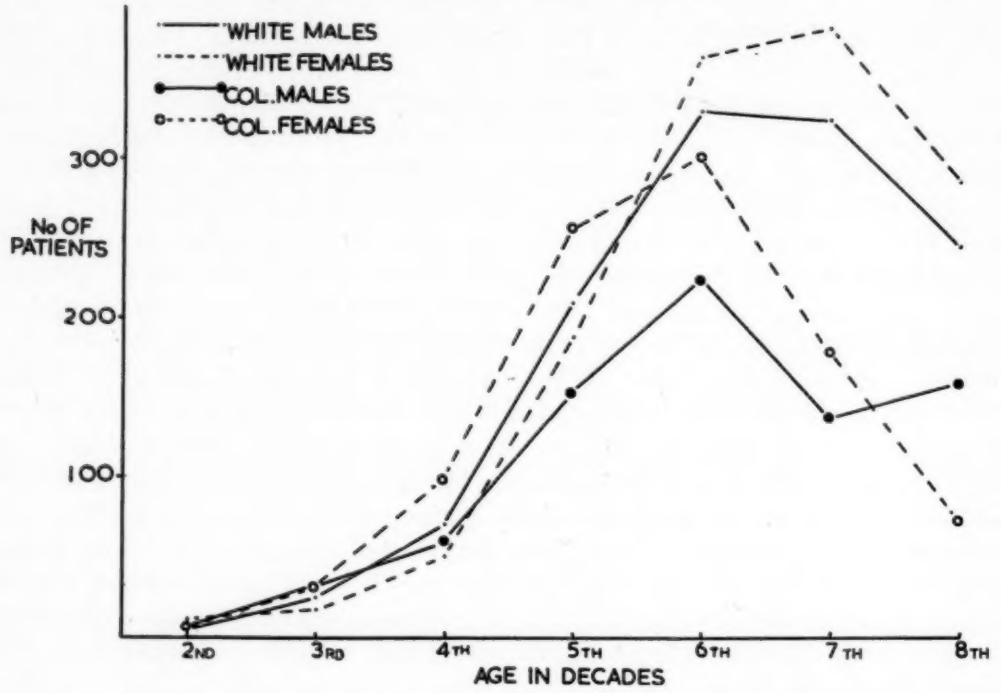

Fig. 1.—The incidence (in decades) of elevated blood pressure, according to sex and age, in the 2,494 White and 1,709 Cape Colored patients over the age of 10 on whom electrocardiograms were recorded. There were 1,202 White males, 1,292 White females, 763 Cape Colored males, and 946 Cape Colored females. An elevated blood pressure is more common in the White female than in the White male after the fifth decade. In the Cape Colored female the incidence is far higher than in Cape Colored male from the fourth to the sixth decades, and is higher than in the rest of the population between the fourth and fifth decades.

When the severity of hypertension is analyzed in the group of patients with hypertension alone (uncomplicated by other forms of cardiac disease), according to race, age, and sex (Figs. 2 and 3), the following results emerge. Using the criteria of electrocardiographic severity (Fig. 2), we find that Cape Colored males are more severely affected than White males, but the age distribution is similar. Cape Colored females, however, far outnumber all other groups, and their hypertension appears at least a decade earlier. This is even more strikingly demonstrated by using the criteria of diastolic pressure (Fig. 3). The Bantu figures have not been included in this analysis because the sex distribution in the "population at risk" is so unnatural, as stated above.

Valvular Disease of the Heart.—The incidence of rheumatic heart disease in 12,512 patients submitted to electrocardiography is approximately 12 per cent, and that of rheumatic fever, 1 per cent (Table VI). Of the 1,552 patients with rheumatic heart disease, 640 (41 per cent) were Whites, 808 (52 per cent)

were Cape Colored, and 104 (7 per cent) were Bantu. Of the 157 patients with rheumatic fever, 68 (43 per cent) were Whites, 79 (50 per cent) were Cape Colored, and 10 (7 per cent) were Bantu. It would appear, therefore, that rheumatic disease is more common in the Cape Colored than in the Whites, and at least as common in the Bantu as in the Whites.

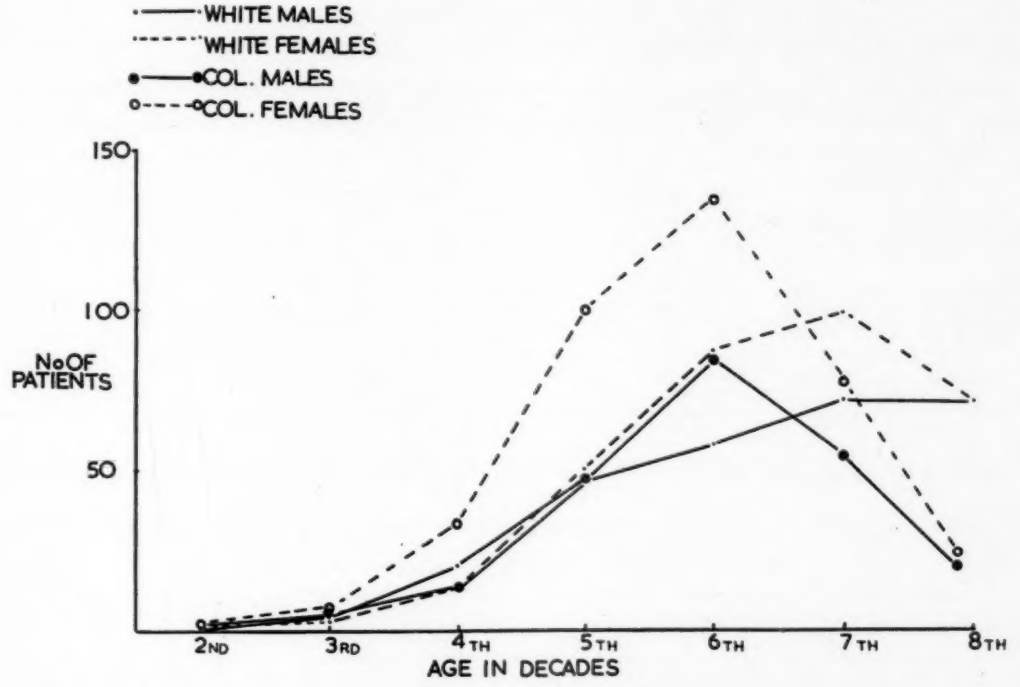

Fig. 2.—The incidence (in decades) of Grade 2 electrocardiographic changes, according to sex and age, in the 1,738 White and 1,325 Cape Colored patients with uncomplicated hypertension. There were 272 White males, 325 White females, 228 Cape Colored males, and 380 Cape Colored females. These electrocardiographic changes are found more commonly in Cape Colored males than in White males, even though the total number of hypertensive White males is greater than that of hypertensive Cape Colored males. Cape Colored females are affected more than all other groups, and severe electrocardiographic changes appear at least a decade earlier.

The incidence of rheumatic heart disease according to age and sex is shown in Table VII. At almost all ages this condition is more common in the female than in the male. The figures for the Bantu show a similar trend up to the age of 30, but after this the males outnumber the females, presumably because of the abnormal sex distribution of the Bantu population,[1] previously described. With advancing age, the Whites outnumber the Cape Colored significantly, and after the fifth decade the disease is relatively uncommon in the Cape Colored and rare in the Bantu.

The incidence of pure valvular disease is found to be 2.5 per cent (320 cases) of the 12,512 patients submitted to electrocardiography, with syphilis responsible for almost 1 per cent (Table VIII). The numbers of Whites and Cape Colored with pure rheumatic valvular disease are approximately equal. When syphilitic valvular disease and aortic aneurysms are analyzed, however, the Cape Colored far outnumber the Whites. The Bantu are well represented in the rheumatic

group and, like the Cape Colored, are far more numerous in the syphilitic group than are the Whites. When the unknown group is added to the rheumatic and syphilitic groups, the disproportionate involvement of the Cape Colored and Bantu patients becomes more manifest. Thus, there were 87 White, 173 Cape

TABLE VI. INCIDENCE OF RHEUMATIC HEART DISEASE AND RHEUMATIC FEVER IN THE THREE RACIAL GROUPS

RACE	RACIAL DISTRIBUTION OF ECGS		RACIAL DISTRIBUTION OF 1,552 CASES OF RHEUMATIC HEART DISEASE		RACIAL DISTRIBUTION OF 157 CASES OF RHEUMATIC FEVER	
	NUMBER	PER CENT OF TOTAL	NUMBER	PER CENT OF TOTAL	NUMBER	PER CENT OF TOTAL
White	7,232	58	640	41	68	43
Colored	4,497	36	808	52	79	50
Bantu	783	6	104	7	10	7
Total	12,512	100	1,552	100	157	100

TABLE VII. SEX AND AGE OF PATIENTS WITH RHEUMATIC HEART DISEASE IN THE THREE RACIAL GROUPS

AGE	WHITES		CAPE COLORED		BANTU		TOTAL
	MALE	FEMALE	MALE	FEMALE	MALE	FEMALE	
0– 9	13	11	20	20	2	2	68
10–19	38	44	71	107	7	12	269
20–29	32	60	74	160	9	19	354
30–39	40	61	49	102	18	14	284
40–49	54	75	33	48	8	7	225
50–59	34	49	36	35	5	—	159
60–69	36	44	8	26	—	1	115
70+	23	26	9	10	—	—	68
Total	270	370	300	508	49	55	1,552

TABLE VIII. RACIAL INCIDENCE OF AORTIC VALVULAR DISEASE

RACE	RACIAL DISTRIBUTION OF ECGS		RHEUMATIC AORTIC VALVULAR LESIONS		SYPHILITIC AORTIC VALVULAR LESIONS		UNKNOWN AORTIC VALVULAR LESIONS	
	NUMBER	PER CENT OF TOTAL	NUMBER	PER CENT OF TOTAL	NUMBER	PER CENT OF TOTAL	NUMBER	PER CENT OF TOTAL
White	7,232	58	60	46.5	19	18	8	9
Colored	4,497	36	59	46.5	65	59	59	71
Bantu	783	6	9	7	25	23	16	20
Total	12,512		128		109		83	

Colored, and 50 Bantu cases. Because many of the unknown group are probably syphilitic in origin, one might conclude that cardiovascular syphilis in the Cape Colored and Bantu is far more common than in the Whites, and that the Bantu is possibly more affected than the Cape Colored (although the figures are small).

When age distribution is considered, 71 of the 128 cases of rheumatic aortic incompetence occurred under the age of 40, and 38 between the ages of 40 and 60 years. Seventeen of the 109 cases of syphilitic valvular disease occurred under the age of 40, and 69 between the ages of 40 and 60 years. Of the 83 cases in the group of unknown aortic valvular lesions 11 occurred under the age of 40, and 44 between ages 40 and 60 years, suggesting that many of these cases were syphilitic in origin.

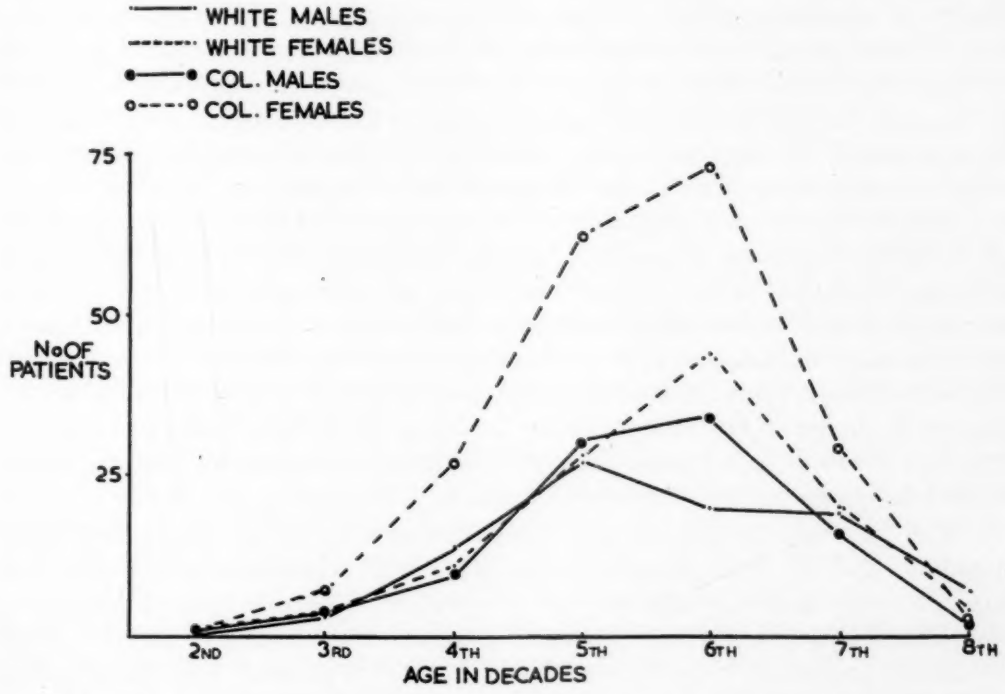

Fig. 3.—The incidence (in decades) of diastolic blood pressures over 130 mm. Hg, according to sex and age, in the 1,738 White and 1,325 Cape Colored patients with uncomplicated hypertension. There were 90 White males, 112 White females, 98 Cape Colored males, and 208 Cape Colored females. Cape Colored males tend to be affected more commonly than White males (especially since the total number of hypertensive White males is greater than the total number of hypertensive Cape Colored males). The strikingly increased incidence in Cape Colored females is well shown. Cape Colored females are affected more than any other group, and severe diastolic hypertension occurs at least a decade earlier.

When the sex distribution is analyzed, males and females are approximately equally affected in White and Cape Colored groups suffering from rheumatic aortic incompetence (33 White males, 27 White females, 29 Cape Colored males, and 30 Cape Colored females). Males outnumber females by 8 to 1 in the Bantu group for the reasons given above. In regard to cardiovascular syphilis males far outnumber females in all races (18 to 1 in Whites, 48 to 16 in Cape Colored, and 22 to 3 in Bantu), with an unusually high incidence in Cape Colored females.

In the group with unknown valvular lesions there were 8 White males and no White females, 33 Cape Colored males and 26 Cape Colored females, 11 Bantu males and 5 Bantu females.

DISCUSSION

Hypertension.—

The effect of environment and geographic conditions on the incidence of hypertension has been studied extensively.[10] Environment appears to have a strong influence on the predisposition to essential hypertension, and this is related to the levels of the blood pressure encountered in the general population.[11,12]

The incidence of hypertension in the Non-White races can be summarized briefly. It would appear that in China there is a tendency for the general population to have a blood pressure lower than that of the general population in North America and Great Britain,[13-20] and this applies also to foreigners in China.[21-23] On the other hand, Chinese who have been resident in Canada for years[24] tend to have pressures similar to Canadian residents. A similar tendency toward low blood pressure is found in India.[25-27] Bays and Scrimshaw[28] reviewed the literature and concluded that geographic and cultural environment had a significant effect on the incidence of essential hypertension, and that racial differences in incidence do indeed exist. A lower blood pressure is found in Koreans, Marshall Islanders, Caroline Islanders, Eskimos, Zuñi Indians, Mexicans, Yucatecans, Guatamalans, Panamanians, San Blas Islanders, and Puerto Ricans than in residents of the United States. In Japan, on the other hand,[29,30] essential hypertension is almost as common in urban Japanese as in Americans, and the incidence of cerebral hemorrhage is extremely high.[30] (Sixty per cent of hypertensive Japanese develop the latter condition.[31])

The incidence of hypertensive heart disease among the White and Negro populations in the United States has been studied extensively. All racial comparisons agree that heart disease is more common in Negroes than in Whites,[32-36] and with hypertensive heart disease a proportion of 2 to 1 is usually given. There also appears to be an increase in the number of patients with hypertension during the years.[37] In a study of apparently healthy men (6,000 prisoners and 400 prison guards) in Kentucky, Alvarez and Stanley[38] found that age had little effect on the blood pressure, but in Negroes there was a higher blood pressure than in Whites, and the pressure tended to rise more rapidly. Allen[39] reported 249 cases of hypertension in a group of 1,000 Negro male workers in Cincinnati, whereas there were only 91 cases in a control group of Whites. Adams,[40] in a routine examination of 6,000 Colored and 8,000 White workers in New Orleans, also found a slightly higher level of blood pressure in Colored than in Whites, and, after the age of 40 years, a more rapid rise in hypertension in the Colored was confirmed. With regard to hypertensive heart disease in a combined study of 623 patients in Virginia and Boston, Wood and associates[32] found twice as many instances in Negroes as in Whites. Stone and Vanzant[33] confirmed this finding in Texas and showed that hypertension tended to occur at an earlier age in the Negro; under the age of 50 years, 50 of their cases were Whites, whereas

118 were Negroes, although the Whites outnumbered the Negroes in the series by 5 to 4. Schwab and Schulze,[34] also in Texas, found the incidence in Negroes to be two and a half times that of the Whites. In Tennessee, Laws[35] found the incidence to be higher in Negroes than in Whites, even though he included arteriosclerosis with hypertension. In Chicago, Flaxman[36] found 57 per cent of 1,646 cases to be hypertensive; 53.6 per cent of the White patients were hypertensive as compared to 60.4 per cent of the Colored. In Kentucky, Weiss and Prusmack[41] compared 1,198 Negro patients with 989 Whites. Hypertension occurred a decade earlier in Negroes, with 414 under 50 years of age, whereas only 146 Whites were under that age. Keselman[42] found hypertension to be 3.1 times as common in the Negro as in the White male prison inmate in every age group.

Pathologic investigations show similar trends. Shapiro,[43] working in Chicago, found as many cases in Negroes as in Whites, but the Negroes showed a far greater incidence of nephrosclerosis with uremia (malignant hypertension). Hedley,[44] in Washington, found hypertension to be especially fatal in Negroes, particularly the females, with an incidence of 89.4 per cent of Negroes as compared with 60.3 per cent of Whites exhibiting arteriosclerotic hypertensive heart disease. Moritz and Oldt,[45] in Cleveland, found 50 per cent more "Blacks" in their series of 200 cases than expected, and "Blacks" died at a younger age than Whites. Peery and Langsom[46] found 519 cases of cardiac disease in 2,066 autopsies in Charleston. Hypertensive heart disease was particularly common in the Negro, who died earlier of vascular disease than the White.

The infrequency of coronary disease in the Negro in comparison with the White is worthy of note.[32,44,46]

An extensive study of blood pressures by Saunders and Bancroft[47] showed that the average pressure of Negroes and Whites was higher in the Virgin Islands than in the United States, that the blood pressure increased with age, and that in Negroes the average pressure tended to be higher than in Whites.

In Africa the information is as yet incomplete. In Egyptians[48] the blood pressures are, on the whole, lower, and, although by no means uncommon, essential hypertension has a somewhat lower incidence than in the West. Donnison[49] investigated 1,000 male natives on the shores of Lake Victoria in Tanganyika under primitive conditions and found that after 40 years of age the blood pressure level tended to become reduced, in contrast to what happens in Whites. During a 2-year period at a native hospital, approximately 1,800 patients were admitted and no case of hypertension was encountered. In the pathologic material available, both atheroma and arteriosclerosis were rare. Jex-Blake,[50] working in Kenya, found hypertension to be common in the Whites, but in 1,100 necropsy studies of Kenya natives, he found no case of calcification or arteriosclerosis of the great arteries of the chest and abdomen. Atheroma of the aorta was common and kidney disease not infrequent. Only one case of cerebral hemorrhage was seen, and this was attributed to syphilis. Vint,[51] in 1,000 necropsies on natives in Nairobi (Kenya) found aortic atheroma in 89 cases. "True nephrosis as represented by the arteriosclerotic kidney is rare in Kenya," he wrote. "The writer has not seen a case of essential hypertension, nor do the medical records

of the Colony show evidence of its occurrence." Only one case of cerebral hemorrhage was encountered. Kröber,[52] also in East Africa, reported a low incidence of hypertension in the native population.

In natives of Uganda, Williams[53] found both "essential" and renal hypertension, but the majority of cases (43 of 66) were renal. Essential hypertension was more common in the Whites and Asians than in the natives. Coronary and cerebral atheroma with hypertension were uncomon. In Liberia, Shattuck[54] found less hypertension in Liberian Negroes than in American Whites.

Not all natives living in Africa have low blood pressures. Reliable data from the Belgian Congo is not available, although there is some evidence that hypertension is not rare.[55] In Salisbury (Southern Rhodesia), Gelfand[56] found an incidence of almost 15 per cent in his 189 cases.

In the South African Bantu, information is available mainly from Johannesburg. Heimann and associates,[57] in a short preliminary study which included 120 Bantu, found 18 cases of "degenerative heart disease" including hypertension. Becker,[58] in his study of 3,000 autopsies during the period 1924 to 1938, found hypertensive heart disease to be "the second commonest disease of the cardiovascular system amongst the Bantu and Colored subjects of South Africa." It was the most common cause of congestive cardiac failure (95 of 332 cases). Ordman[59] made a survey of 1,522 apparently healthy male and female Bantu subjects and found a high incidence of hypertension, with a rise in pressure with age. There was no racial or tribal correlation of hypertension, but there was an association between hypertension and overweight. Uys[60] found 76 cases showing evidences of hypertensive nephrosclerosis in 3,707 consecutive Bantu autopsies, 23 of which showed malignant nephrosclerosis. Of the cases in the group with benign nephrosclerosis 35.8 per cent died of cardiac causes and 31.1 per cent of cerebral. He felt that hypertension is slightly less common in the Bantu than in the Whites but more explosive in type, frequently accompanied by death in renal failure. On the whole, Bantu subjects tended to die a decade earlier than Whites suffering from hypertension.

The data obtained in the present study show that the incidence of hypertension is high in both the Non-Whites and Whites. It must be accepted, however, that a single blood pressure may not be a true reflection of the presence or absence of systemic hypertension. Moreover, the true incidence of hypertension cannot be obtained by an assessment of the number of electrocardiograms requested, since it is not the practice of physicians or surgeons on the hospital staff to have electrocardiographic investigation performed on every patient who has an elevated blood pressure. Nevertheless, these errors are probably cancelled out when a comparison between three racial groups is made, even though the wealthier White members of the population are officially barred from attending the hospital. The number of White and Cape Colored patients who actually attend is approximately equal,[1] and the number of Whites and Cape Colored that comprise the population of Cape Town is also approximately equal.[1] These two racial groups are, therefore, probably comparable. Systemic hypertension commonly complicates coronary vascular disease,[61-64] and coronary vascular disease occurs far more commonly in the Whites than in the Cape Colored.[1-4]

Hence, in an analysis of all electrocardiograms taken one would expect to find a higher incidence of hypertension in the Whites than in the Cape Colored. Whether this signifies a true increased incidence in the Whites is doubtful however. The incidence of hypertension is at least as common in the Bantu as in the Whites, judging from the data presented. When it is remembered that the male Bantu far outnumbers the female and that the older group is poorly represented, the significance of the findings increases. The true incidence of hypertension in the Bantu may, in fact, exceed that in the Whites.

The severity of hypertension as assessed on the basis of electrocardiographic criteria is greater in the Cape Colored and the Bantu than in the Whites (Tables III-V; Figs. 1-3). Electrocardiographic changes have been found to be related to the severity of hypertension. Thus, Perera[65] found the average life expectancy in patients with hypertension to be 19 years, but when the presence of "myocardial damage" was demonstrated by the electrocardiogram, this expectancy was reduced to 7 years. Bechgaard[66] found a mortality of 60 per cent in patients with an abnormal electrocardiogram, as compared with a mortality of 20 per cent in patients with normal patterns. Daley and associates,[67] Oppenheimer,[68] Rasmussen and Bøe,[69] and Griep and associates[70] have also reported that the presence of electrocardiographic abnormalities affect the prognosis adversely. According to Fishberg,[71] "the vast majority of patients with essential hypertension detected incidentally and without symptoms have normal electrocardiograms," whereas "the large majority of patients with symptoms actually correlated with essential hypertension have abnormal electrocardiograms."

Similarly, the height of the diastolic pressure has a distinct bearing on the prognosis of hypertension.[65,66] Frant and Groen,[72] in a follow-up study of 418 patients with hypertension, found that the mortality increased with the increase of both systolic and diastolic blood pressure, and his findings correlated well with those of Lian.[73] The severity of hypertension based on the height of the diastolic pressure in this series also indicates that hypertension is more severe in the Cape Colored and Bantu than in the Whites.

That females predominate over males in the incidence of hypertension, and tolerate the condition better, has been the feature of most reported series. This was well shown in a comprehensive survey by Woolsey.[74] Similar findings have been reported by others.[72,75-78] In the present series, females predominated both in the White and the Cape Colored groups. A striking finding has been the tremendous predominance of Cape Colored females over all other groups and the occurrence of severe grades of hypertension at a far earlier age. This is not related to toxemia of pregnancy, since the incidence in the Cape Colored population of Cape Town is no higher than that in the White population.[79] Very few patients suffering from toxemia of pregnancy are included in this series, because there are no maternity wards or antenatal clinics at this hospital. Therefore, the figures probably truly reflect a high incidence of the condition in the Cape Colored female.

Although originally descended from West African Negroes, present-day American Negroes probably differ considerably from their African forebears. They are not strictly comparable with the Cape Colored, because the latter have

little Bantu admixture; nor are they comparable with the Sough African Bantu, who have little, if any, White admixture. Nevertheless, the incidence and tempo of hypertension in the American Negro appears to be very similar to that in the Cape Colored and Bantu. Hypertension is more common in the American Negro than in the Whites, and the data in this study suggest that it is probably as common in the Cape Colored and Bantu as in the Whites in Cape Town. Hypertension appears to be more severe in the Non-White races of Cape Town than in the White race and occurs at an early age, particularly in the Cape Colored female. This seems to be the case, too, with the American Negro.

Valvular Disease of the Heart.—

Rheumatic fever and its most important complication, valvular disease of the heart, is widespread throughout the world, and its prevalence is considerably influenced by climatic conditions. It is rather generally agreed that the disease is common and severe in temperate zones and less common in warmer subtropical and tropical climates.[80]

Although rare in tropical areas, the disease is by no means unknown. In tropical Australia, Cooper[81] found acute rheumatic fever relatively common, but the incidence was lower than in the southern temperate areas. In India, Clarke[82] reviewed the data available up to 1915. He stated that rheumatic fever and rheumatoid arthritis did not occur in the Malayan peninsula and was extremely uncommon in the tropics. Only 14 cases of rheumatic fever had been reported in over 130,000 patients, and 2 of these occurred in Nyasaland. In 281 autopsies in Calcutta, no case of rheumatic heart disease had been found. In 1928, Rogers[83] reported on 4,800 necropsies in India; only 1 case of rheumatic carditis was found. He regarded mitral valve disease as rare clinically.[84] However, more recently, Raghavan,[26] on the basis of necropsy material, regarded the condition as not very uncommon. In Colombo, moreover, both the necropsy and clinical incidence of rheumatic heart disease was little different from that in temperate climates.[85]

In the United States and Canada, the disease is common and progressively increases in incidence from the southern to the northern regions of the continent.[86-90] Evidence of a racial susceptibility or resistance to the disease is conflicting. Thus, Negroes have been reported to be less susceptible than Whites,[33,35,91-93] more susceptible,[32,36,91] and equally susceptible.[34,46] It would appear that the Negro does not acquire the disease more readily, but that the mortality rate from rheumatic heart disease is higher than average in the Negro race.[80]

In Africa the information is incomplete. Shattuck[54] found no evidence of rheumatic fever or carditis in Liberian Africans. In the French colonies it was reported as rare.[94] Donnison,[49] in two years' experience with natives on the shores of Lake Victoria, found no case of rheumatic fever. In Uganda, Fleming[95] reported 7 cases of mitral stenosis in two years. Also in Uganda, Williams[96] found acute rheumatic fever to be rare, and when it did occur, it was seldom of a florid nature with pericarditis and fever. Chorea practically never occurred. Mitral stenosis, on the other hand, was not rare, 18 patients with pure mitral

stenosis, and 3 with auricular fibrillation being described. In 894 necropsies 13 cases of chronic, nonsyphilitic endocarditis were encountered. Vint[51] described 6 cases of rheumatic valvular disease in his necropsy material.

In South Africa the available evidence again comes from Johannesburg. Rheumatic heart disease is not uncommon in the Non-White population. Heimann and associates[57] found 42 cases in the Bantu, comprising 35 per cent of their 120 cases. Becker,[97] on the basis of necropsy evidence, found rheumatic heart disease "as common amongst the Bantu and Colored subjects as in other races in other parts of the world." It was found in 8 per cent of all cases of organic heart disease. Incidence in regard to age and sex did not appear to differ in any way from the condition as seen in other parts of the world. An analysis of the causes of congestive cardiac failure showed it to be responsible for 24 per cent of his 332 cases.

The electrocardiographic data in this study show that rheumatic fever and rheumatic heart disease are common in all three racial groups, and that these diseases appear to be more common in the Cape Colored than in the Whites. The Bantu are probably more affected than the Whites. Females acquire the disease more commonly than do males, as is the usual finding elsewhere.[98-100] It is well known that social and economic factors play a large part in the development of rheumatic heart disease.[101-105] Overcrowding,[106,107] exposure to cold and damp,[104,108-110] and malnutrition[111] are recognized as important factors. The impression of most physicians on the Groote Schuur hospital staff who are also in private practice is that rheumatic heart disease is far more common in the poorer Whites attending the hospital than in the wealthier Whites; this correlates with the findings reported by Rinehart,[111] who quoted an incidence of 13.1 per cent rheumatic patients attending an outpatient department, as compared with 0.7 per cent in 700 patients from private practice. The Cape Colored and Bantu members of Cape Town's population are underprivileged, and overcrowding, exposure, and malnutrition are the usual findings. It is not surprising, therefore, to find rheumatic disease more commonly in these two racial groups. The preponderance of Cape Colored over Whites becomes more manifest if one considers patients under the age of 40 years (783 to 327), because after this age the incidence in the Cape Colored drops (and almost disappears in the Bantu). This suggests that the Non-White races are more severely affected by rheumatism and that they die earlier. Their economic situation is also such that they cannot support the strain of chronic ill health and loss of earning capacity so well as the Whites.

Race and socioeconomic status has a well-known influence on the incidence of cardiovascular syphilis. Thus, in the United States this disease occurs more commonly among those lowest in the social and economic order and is found far more often among Negroes than Whites. Figures vary from 2:1[33,43,112] to 4:1, and over.[32,34,36,44,46,113] In Africa, in general, syphilis of the heart is the commonest cause of valvular disease. In Uganda, Williams[114] found an incidence of 10 per cent (86 of 894) of syphilitic aortitis in his necropsy series. A lower incidence at necropsy was found in Kenya,[51] although cases of syphilis still outnumbered cases of rheumatic heart disease by 4 to 1, but in Tanganyika[49] it was rare.

Heimann and associates,[57] in their clinical series of Bantu in Johannesburg, found 31 cases of syphilitic heart disease, as compared with 42 cases of rheumatic heart disease. Becker[115] found 176 cases of syphilitic heart disease and 106 of rheumatic heart disease in 1,896 routine necropsies on Bantu and Cape Colored in Johannesburg from 1924 through 1938. Rheumatic heart disease was however, a more common cause of congestive cardiac failure (78:55 in 332 cases).

From the electrocardiographic data presented in the present report the incidence of syphilitic heart disease in the Cape Colored and Bantu far exceeds that in the Whites. As opposed to the finding in the Whites (or Cape Colored), syphilis is a far more common cause of heart disease in the Bantu than is coronary vascular disease.[1] The age distribution of cardiovascular syphilis is similar to that reported elsewhere,[116] the peak incidence occurring in the fourth to sixth decades. Males far outnumber females, as in all series.[33,34,44,46,112,117] The high incidence of syphilitic heart disease among the Non-White races is probably related to the high incidence of syphilis in these groups and not to an inherent weakness of the cardiovascular apparatus.

SUMMARY

1. The aim of this study was to determine the interracial incidence of hypertension and of valvular disease of the heart in patients attending Groote Schuur Hospital, Cape Town, during the years 1952 through 1956. Analyses of 12,512 electrocardiograms of adults (over the age of 12 years) were made according to the clinical diagnoses and casual blood pressures recorded on the request forms.

2. An elevated blood pressure was found in approximately one third of the patients. Unlike the findings in regard to coronary vascular disease there was no disproportionate increase in incidence among the Whites.

3. Hypertensive disease as assessed by electrocardiographic criteria of severity and by the height of the diastolic pressure was more severe in the Cape Colored and Bantu than in the Whites.

4. Hypertensive disease occurs at an earlier age in the Non-White races than in the Whites. Females are affected more frequently than males, and Cape Colored females, in particular, develop hypertension at an earlier age than all others, and it is of a far severer degree.

5. Rheumatic heart disease occurred in approximately one eighth of the patients. It was more common in the Cape Colored than in the Whites, and at least as common in the Bantu as in the Whites. Females are affected more commonly than males, and the majority of cases occur under the age of 50 years. The disease appears to be more severe in the Cape Colored and Bantu than in the Whites, since after the age of 40 years far fewer cases are found in the Cape Colored and Bantu than in the Whites.

6. Syphilitic heart disease is far more common in the Non-White races than in the Whites, and males are affected several times more frequently than females. The peak incidence is between the ages of 40 and 60 years.

7. The significance of these findings is discussed and they are correlated with the findings on these diseases in other countries.

I wish to thank the Staff of Groote Schuur Hospital and Dr. A. Landau of the New Somerset Hospital for their cooperation throughout, and my colleagues in the Cardiac Clinic, Dr. L. Vogelpoel and Dr. Maurice Nellen, in particular. My thanks are also due to Dr. C. Merskey for his criticisms, and to Mrs. C. M. Hall for her assistance in the analysis of the data.

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Situs Inversus Totalis Associated With Complex Cardiovascular Anomalies

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It is well known that severe and bizarre cardiac abnormalities can accompany situs inversus. The incidence of total situs inversus has been estimated as only 1 in 10,000 in the entire population of the western nations, while partial inversion of one or more organs occurs more commonly. The frequency of associated cardiovascular malformations in situs inversus totalis is relatively low, approximately 8 per cent, compared to isolated dextrocardia with a 25 per cent incidence of cardiac anomalies.[4] In the past, study of these grossly malformed hearts has been restricted largely to postmortem examinations. With recent advances in surgery, accurate anatomic and functional analysis is necessary if repair of the cardiac lesions is to be attempted in these patients. It is the purpose of this report to present 2 cases of situs inversus totalis with complex cardiovascular malformations, in which these defects were evaluated by clinical findings, cardiac catheterization, and angiocardiography. Embryologic aspects and the wide variations of associated cardiovascular anomalies which may be found in situs inversus totalis will be discussed briefly.

CASE REPORTS

CASE 1.—S.M.B., a 5-month-old white female, was noted at birth to have rapid respirations, cyanosis, and a cardiac murmur. The tachypnea subsided after about one month, and general growth and development were normal, but the baby continued to become markedly cyanotic with crying or exertion. The remainder of the past history and the family history were noncontributory.

On physical examination, developmental and nutritional status appeared normal for her age. Blood pressures varied between 50 and 60 mm. Hg (flush) in both arms and legs. Cyanosis, minimal at rest, increased with crying. The lungs were clear. The heart, located in the right chest, was not enlarged, and a faint thrill was palpable at the right upper sternal border. A long, blowing, Grade 4 systolic murmur, heard along the entire right sternal border, was transmitted over the precordium and to the right back. The second sound at the pulmonic area (right second intercostal space) was single and of normal intensity. The liver edge was palpable at the left costal margin, and a stomach bubble was noted in the right upper quadrant. The remainder of the physical examination was noncontributory.

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Laboratory findings included a hemoglobin of 14.7 Gm., a red blood cell count of 5,970,000, and a packed cell volume of 49 per cent. The electrocardiogram revealed marked right axis deviation with vertical position, which was suggestive of marked right ventricular hypertrophy and possible left ventricular hypertrophy. Roentgenograms showed a complete situs inversus, a large thymus, a boot-shaped heart, and decreased pulmonary vascularity.

At cardiac catheterization (Table I) the catheter was passed first into an overriding aorta, and later through a tight pulmonic stenosis. In addition to right ventricular hypertension, an atrial oxygen step-up was noted. The angiocardiogram showed an interventricular septal defect with filling of the aorta from the right ventricle, pulmonic valvular and infundibular stenosis, and an anomalous pulmonary vein draining into the superior vena cava (Fig. 1). Furthermore, an anterior location of the aorta and systemic ventricle and a posterior displacement of the pulmonary artery were noted.

It was decided to postpone operation until polycythemia or other difficulties make it necessary. At such time, a complete repair of the cardiovascular defects will be attempted, using extracorporeal circulation.

TABLE I. CARDIAC CATHETERIZATION OF PATIENT S.M.B., OCT. 25, 1957*

SITE	PRESSURE (MM. Hg)	OXYGEN SATURATION (%)
Right pulmonary artery	23/13	79
Main pulmonary artery	19/13	78
Aorta	94/72	79
Right carotid artery	100/85	78
Right ventricle (average)	95/7	80
Right atrium (average)	11/7	82
Inferior vena cava	11/8	69
Superior vena cava (high)	12/5	68

***Impression:* Left-to-right atrial shunt; interventricular septal defect with right-to-left shunt; pulmonic stenosis.**

TABLE II. CARDIAC CATHETERIZATION OF PATIENT P.G., AUG. 12, 1955*

SITE	PRESSURE (MM. Hg)	OXYGEN SATURATION (%)
Pulmonary artery not entered	———	—
Right ventricle (mid)	53/–6	87
Right atrium	9/–2	80
Superior vena cava (on right)	4/–2	79
Femoral artery (cuff)	108/72	98

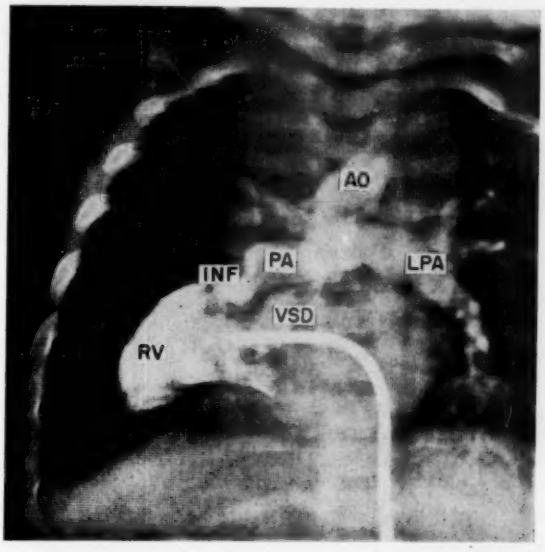
***Impression:* Dextrocardia; interventricular septal defect with left-to-right shunt; pulmonary hypertension.**

CASE 2.—P.G., a 15-year-old white girl, had been well until she developed pneumonia at the age of 9 months. Roentgenographic studies at that time revealed complete situs inversus. She remained asymptomatic until 8 years of age, but since then has had inordinate fatigue and dyspnea on exertion.

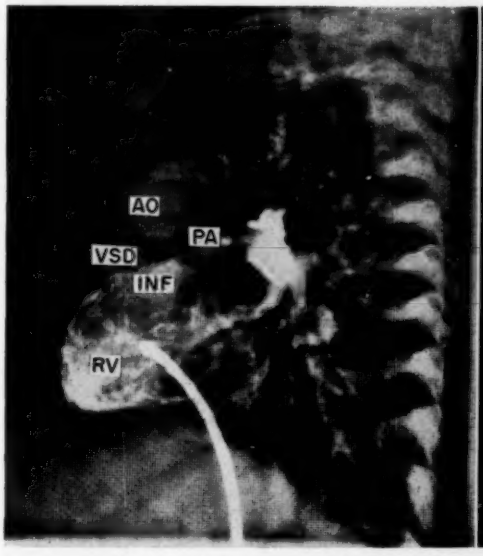
On physical examination in December, 1957, a moderate thrill was maximal in the fourth intercostal space, to the right of a bulging sternum. The area of cardiac dullness, located in the right chest, was enlarged to percussion. A Grade 4, harsh systolic murmur was heard at the lower sternal area. This murmur was transmitted to the right-sided apex, over the entire precordium, down the right arm, and to the back. This murmur merged with an early, short decrescendo,

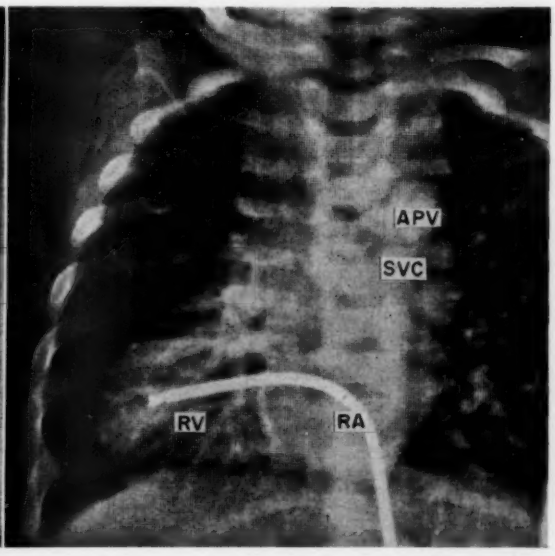
Grade 2 diastolic murmur along the right upper sternal border. The second sound was increased in the right second intercostal space (pulmonic area), as compared with that heard in the left second intercostal space.

Electrocardiographic findings consisted of mirror-image dextrocardia (Q wave with inversion of all waves in Lead I), a wandering auricular pacemaker, and probably combined ventricular hypertrophy. Chest roentgenograms (Fig. 2,*A*) demonstrated marked convexity of the sternum, combined ventricular hypertrophy, and increased pulmonary vascularity.



A.

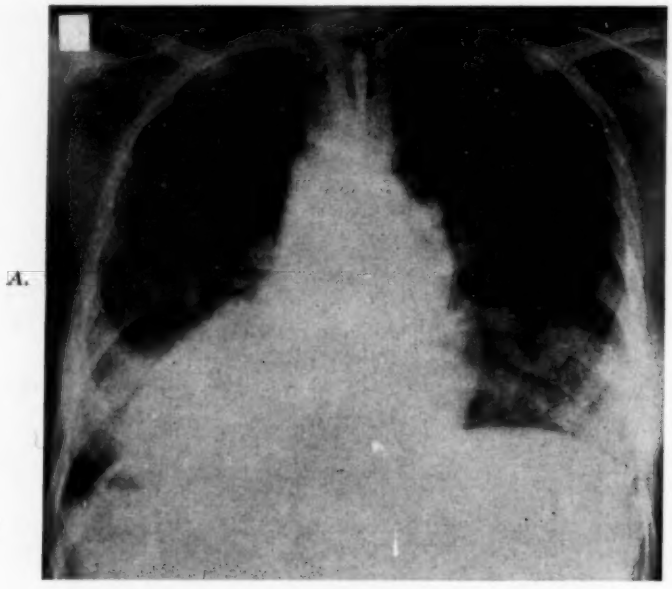




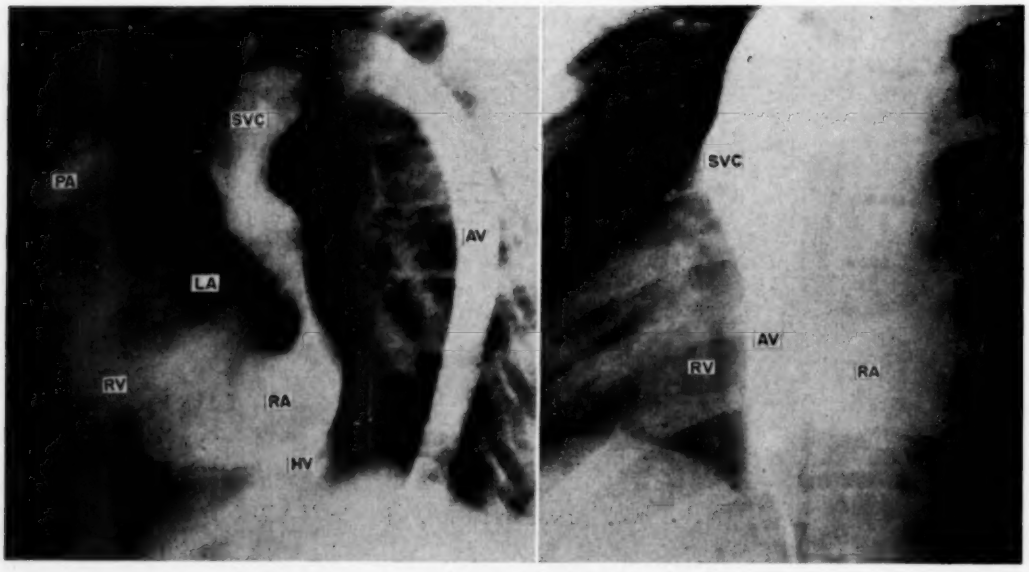
B. *C.*

Fig. 1.—Case 1, S. M. B.: Serial angiocardiographic views following selective injection of 50 per cent Miokon into the right ventricle. *A*, Contrast media outlining the enlarged right ventricle (*RV*), passing through an area of infundibular narrowing (*INF*) into the pulmonary arteries (*PA*), and shunting through a ventricular defect (*VSD*) into a left-sided aorta (*AO*). *B*, Lateral view of *A*, showing, in addition to the above, an anteriorly located systemic ventricle and aorta. *C*, A later film showing filling of the superior vena cava (*SVC*) and right atrium (*RA*) from an anomalous left pulmonary vein (*APV*).

Cardiac catheterization (Table II) in August, 1955, revealed a right ventricular pressure of 53/-6 mm. Hg in the presence of a moderate left-to-right ventricular shunt. The pulmonary artery was not entered, and angiocardiography was not performed because of extreme cardiac irritability.



A.



B. C.

Fig. 2.—Case 2, P. G.: *A*, Posteroanterior roentgenogram showing situs inversus, combined ventricular hypertrophy, and increased pulmonary vascularity. *B*, Lateral angiocardiogram showing a greatly enlarged azygous vein (*AV*) emptying into the superior vena cava (*SVC*). The column of contrast media is compressed by the enlarged unopacified left atrium (*LA*), and then flows successively into an enlarged right atrium (*RA*), right ventricle (*RV*), and pulmonary artery (*PA*). *C*, Anteroposterior view of *B*, showing the azygous vein (*AV*) coursing upward behind the heart, and then diagonally down and left to empty into the right atrium (*RA*).

In December, 1957, a repeat catheterization was attempted, but the femoral and saphenous veins could not be located. A deep vein was exposed below the inguinal ligament and was entered with a No. 7 Goodale-Lubin catheter. It was found, however, that the usual catheterization could not be performed since the catheter would pass neither to the right nor to the left, but consistently passed through the heart into the superior vena cava, and then curved downward. The reason for this became evident after viewing the angiocardiograms done with selective injection of dye at the lower cardiac border. The contrast media* entered a posteriorly located, greatly dilated azygous vein, which joined the superior vena cava as it entered the venous atrium (Fig. 2, *B* and *C*). Absence of the inferior vena cava was evident from the missing femoral or saphenous vein and from the presence of the greatly dilated azygous vein, which provided for the venous return from the lower half of the body.

The patient was operated upon with the aid of cardiopulmonary bypass on June 6, 1958.† The operative findings consisted of: situs inversus, ventricular septal defect, patent ductus arteriosus, left and right superior vena cava, absent inferior vena cava, and enlarged azygous vein. The hepatic veins drained directly into the venous atrium. There was a gradient of 20 mm. Hg across the aortic valve, and minimal poststenotic dilatation of the left lateral surface of the aorta.

The patent ductus arteriosus was closed by multiple-suture ligation, and the 1-cm. ventricular septal defect, located high under the septal leaflet of the tricuspid valve, was closed with interrupted sutures. Since inspection of the aortic valve revealed no evidence of obstruction, no corrective procedure was necessary. The operation was successful, and the patient's postoperative course has been excellent.

DISCUSSION

Before the recent advances in cardiovascular surgery, embryologic studies of congenital heart anomalies remained almost entirely within the domain of anatomists and pathologists. These advances have made it necessary, however, for clinicians to gain better understanding of the embryology of developmental cardiac anomalies. At present, there is a definite trend to place more emphasis on the dynamics of prenatal development, since an adherence to purely static and descriptive principles will not permit comprehension of ontogenesis and dysontogenesis. Lack of knowledge of the time of disruption of normal embryonic development adds to the difficulties in studying the embryologic basis of congenital cardiovascular abnormalities. Our knowledge concerning these problems has been advanced through the investigations of Spitzer,[30] Pernkopf,[25] and Bredt,[5] and in recent years through the work of Doerr,[7-11] in Germany, and Shaner,[28,29] Edwards,[13,14,21,33] and Patten,[24] in this country. For the purpose of this discussion, situs inversus and the associated anomalies shall be considered separately.

Situs Inversus.—Although Aristotle[2] is credited with the first description of situs inversus in animals, detailed accounts of this anomaly in man have appeared only since the seventeenth century. Küchenmeister,[20] in his extensive monograph on situs inversus, mentions Marcellus Leccius, in 1643, as the first pathologist who performed an autopsy in a case of situs inversus. Since that time, many cases have been reported, with an elaboration on morphologic and embryologic aspects of this abnormality. Until the publication of the works of Wolff,[34] in 1759, and von Haller,[17] in 1768, discussions regarding the etiology

*Miokon (sodium diprotrizoate): manfactured by Mallinckrodt Chemical Works, St. Louis, Mo.
†Operation was performed by James V. Maloney, Jr., M.D.

of this anomaly were centered mainly on mythical speculations. During the nineteenth century, several theories were advanced to explain the pathogenesis of situs inversus. The majority of these theories attributed the inversion of the viscera to faulty local arrangement of one or more organs in the earliest periods of development, which resulted in an inversion of all organs. None of these hypotheses explains situs inversus satisfactorily. Two other theories deserve to be outlined more specifically: (1) In the "monster theory" the occurrence of situs inversus was felt to be closely related to the development of double monsters. According to Förster[16] and Serres,[27] the monster on the right side is always characterized by situs inversus, single cases of situs inversus representing the surviving right monster, the left one having undergone intrauterine destruction. Martinotti,[23] in 1888, and Lochte,[22] in 1894, presented many instances of double monsters without situs inversus. (2) In von Baer's theory of rotation,[3] situs inversus is believed to be due to rotation of the embryo to the right instead of to the left side, so that the yolk sac is located on the right of the embryo. The first-mentioned theory has been abandoned, but von Baer's hypothesis has gained wide recognition. In a recent case report, Fernandez[15] explains situs inversus with this theory.

Specific knowledge concerning the etiology of situs inversus is very limited. It is the current opinion that certain changes of the structural relationships within the ovum or the zygote are responsible for the occurrence of this anomaly.

Associated Anomalies.—In classifying the first patient (S.M.B.) as a case of situs inversus totalis, the question arises as to whether this represents a true example of the anomaly, because the intrathoracic situs of the great vessels is characterized by a left-sided aortic arch and left descending aorta. (An abnormally placed aortic arch and descending aorta can also occur in tetralogy of Fallot without situs inversus.) From the results of the diagnostic procedures outlined above, we are not in a position to state which ventricle is located in the anterior position. If we assume that the anteriorly located aorta is connected to a ventricle which has the internal structure of the systemic ventricle, the diagnosis of an anatomically corrected transposition in the presence of an isolated inversion of the ventricles should be made, since under the condition of situs inversus totalis the atria are in their proper position. If the anterior ventricle has the internal structure of a right ventricle, however, an anatomically uncorrected transposition would be present. It is beyond the scope of this paper to discuss the theories concerning the morphogenesis of these anomalies specifically. Doerr[7-11] has given a detailed account of these problems in his monographs and publications.

Findings similar to those in the second patient (P.G.) were reported by Herboldt,[18] in 1830, and by Virchow,[32] in 1861. In 1909, Schelenz[26] recorded three instances of situs inversus totalis in which the inferior vena cava was absent and, in compensation, the azygous vein had enlarged; he also added one case which he had encountered at autopsy. He stated that when the inferior vena cava is absent, the hepatic veins always drain directly into the right atrium. Angiocardiographic and surgical findings in this patient indicated also that the hepatic veins emptied directly into the venous atrium.

The isolated drainage of the hepatic veins into the right atrium is of considerable practical importance in cardiac operations performed with the aid of hypothermia or extracorporeal circulation. With absence of the inferior vena cava, it is essential that the posterior and inferior aspects of the right atrium be explored. Usually, hepatic veins unite into one large vessel before entering into the right atrium. Occlusion of this venous return as well as superior vena caval flow is necessary in surgical procedures involving hypothermia, since cannulization must be performed when cardiopulmonary bypass is used. Otherwise, a large amount of venous blood will be lost during open heart surgery, and the visualization of the cardiac defect will be greatly impaired.

The intricate pattern of the development of the venous system, especially of the inferior vena cava, results in a formation of anomalous venous pathways more often than is appreciated by clinicians. Huntington and McClure[19] described 15 different types of inferior venae cavae which can occur in the lumbar region as a result of the combinations between the right and left posterior and the right and left supracardinal veins. Of these, all but three types have been observed in the adult cat by these authors. Since the basic plan of the embryonic venous system is essentially the same in man as in the cat, it would be possible for any one of these 15 anomalous types to persist in man. The absence of the inferior vena cava and its replacement by the azygous vein, as occurred in Case 2, is the result of persisting right common cardinal and supracardinal veins, both of which disappear in normal development between the seventh and eighth week of gestation.

Reports of similar cases[1,6,12,31] of absent inferior vena cava, with replacement by the azygous vein, reveal a frequent association with partial or complete situs inversus, persistent left superior vena cava, cor biloculare, pulmonic stenosis or atresia, and atrial and ventricular septal defects. Absence of the inferior vena cava has been reported as an isolated lesion by Downing.[12] In his cases, roentgenograms showed a small rounded density in the superior mediastinum, which represents the dilated, anteriorly coursing azygous vein entering the superior vena cava. This was not noted in Case 2 (Fig. 2,*A*).

SUMMARY

Two cases of situs inversus totalis complicated by complex cardiovascular anomalies are presented. In Case 1 the associated cardiovascular abnormalities consisted of an anteriorly located aorta and systemic ventricle, ventricular septal defect, pulmonic stenosis, and partial anomalous pulmonary venous drainage, while in Case 2 a ventricular septal defect and an absent inferior vena cava with functional replacement by the azygous vein were diagnosed. Cardiac catheterization and angiocardiography were utilized in order to obtain accurate preoperative anatomic and functional data.

Embryologic aspects and the various cardiac anomalies associated with situs inversus totalis are discussed.

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Human Hypertension Due to Thrombotic Occlusion of Both Renal Arteries: Report of a Case "Cured" by Surgical Removal of the Thrombus

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INTRODUCTION

There have been a number of reports of severe arterial hypertension secondary to unilateral renal ischemia, in which the ischemic kidney remained capable of elaborating a pressor substance whose release into the general circulation was the cause of the disease.[2,3] Bilateral renal ischemia has been reported in abdominal coarctation of the aorta.[5] Frequently, however, bilateral renal artery disease leads to early complete interruption of the renal blood supply or renal infarction and death due to renal insufficiency. The following case presents the unusual feature of bilateral partial occlusion of both renal arteries producing bilateral renal ischemia with severe hypertension in an acute form. The phase of renal insufficiency lasted for a relatively prolonged period of time, and thus permitted the correct diagnosis to be established. The patient was eventually "cured" by surgical removal of the obstructing thrombotic lesion.

CASE REPORT

The patient was a 59-year-old white man, a farmer and cattle raiser, who had been in good health until approximately 1948. At that time he noticed increased fatigability and pain in both calfs when walking on his farm. This promptly subsided after rest. These symptoms progressed insidiously during the next 8 years, until it was impossible for him to walk more than 10 yards. He had been a chronic dyspeptic for the past 15 years, and as far back as he could remember, he had always had indigestion. He noticed heaviness after meals and vomited occasionally. His personal physician had treated him for "chronic gastritis," and x-ray studies of the gastrointestinal tract had shown "hypertrophy of the gastric mucosa and a spastic condition of the pylorus." His blood pressure during the past 10 years ranged between 140 and 150 mm. Hg systolic and 80 and 95 mm. Hg diastolic. The patient had smoked heavily for the past 30 years (three packs of cigarettes and one to three cigars a day).

On Nov. 5, 1957, his personal physician was summoned urgently because of an unexpected and particularly alarming acute pulmonary edema, which recurred twice within the next 48 hours. In this condition he was referred to the hospital for further studies and treatment. At the time of entrance into the hospital the patient appeared as a well-developed, muscular man, critically

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ill. He was orthopneic, breathing with difficulty; respirations were 35 per minute. Temperature was normal. There was a moderate muscular atrophy with loss of hair on both legs. Temperature of both feet appeared normal. Cardiovascular examination showed a heaving apex beat that could be felt 5 cm. outside the mid-clavicular line. There was a ventricular gallop at the apex and a Grade 3 blowing systolic murmur, best heard between the apex and xiphoid. Blood pressure in both arms was 250 mm. Hg systolic and 140 to 150 mm. Hg diastolic. Pulsations were absent in both femoral, popliteal, and dorsalis pedia arteries, and no pressure was obtained in the legs. The pulse was regular at 100 per minute. Examination of the eye grounds revealed spasm of the vessels, arteriovenous compression, exudates, and hemorrhages. The left eye ground in particular presented an extensive hemorrhage. The respiratory system showed numerous moist râles and rhonchi on auscultation. The abdomen was soft and no masses could be palpated. The liver was moderately enlarged and could be felt 4 cm. below the costal border. The spleen was not enlarged. Exploration of the nervous system and family history were not contributory. The electrocardiogram at this time showed sinus tachycardia, left axis deviation, and inverted T waves in Leads I and aV_L and V_6, deeply inverted in Leads V_3 to V_5. The tracing suggested left ventricular enlargement and myocardial changes.

Radiologic studies of the chest (Fig. 1,*A*) showed a diffuse, ill-defined shadow involving both hili and extending into the right lung field. There were patches in both lung bases and in the left lung field with signs of pulmonary congestion. The radiologic picture was consistent with the diagnosis of acute pulmonary edema. A plain film of the abdomen in various positions failed to show any abnormality of the kidney or urinary tract. The blood count was 4.9 million red cells, 16,000 white cells, 77 per cent neutrophils, 1 per cent eosinophils, 12 per cent lymphocytes, and 10 per cent monocytes. Hematocrit was 40 per cent. Sedimentation rate (Westergren) was 60 mm. the first hour, and 100 mm. the second hour. Blood urea was 85 mg. per cent, and glycemia was 85 mg. per cent. Urinalysis showed a trace of albumin, density 1,020; 18 white cells, 3 red cells, and a few hyaline casts. Catecholamines in the urine were normal. Diuresis was considerably reduced and fluctuated between 200 and 500 c.c. per day.

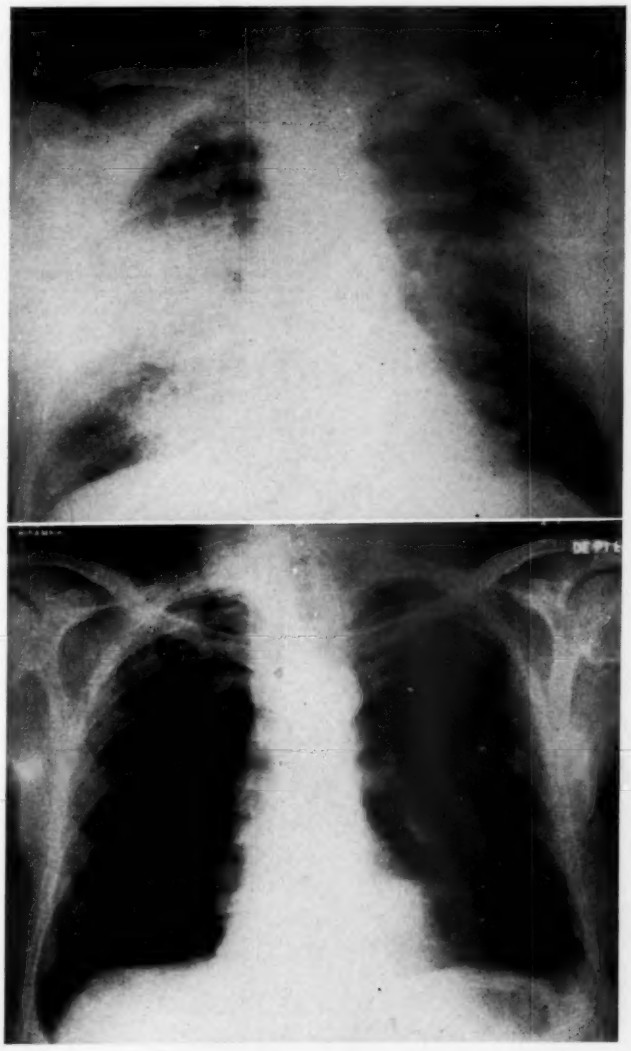
Early treatment consisted in absolute bed rest, sedatives, oxygen, full digitalization, papaverine, fluid and electrolyte control, sodium restriction, and diuretics. It was considered that the patient had extensive arteriosclerosis, arteriosclerotic heart disease, and intermittent claudication due to chronic aorto-iliac thrombosis (Lerich's syndrome), and that he had entered upon a malignant phase of hypertension. During the first 2 weeks at the hospital the blood pressure level was unstable and fluctuated from 230 to over 300 mm. Hg systolic and from 130 to 160 mm. Hg diastolic, and the patient suffered numerous attacks of acute pulmonary edema during the rises in blood pressure. This paroxysmal hypertension with acute pulmonary edema was controlled with difficulty with the usual measures of morphine, aminophylline, strophanthin, alcohol vapor, and slowing of the venous return from the extremities. During this phase of the observation, while the patient was under digitalis treatment, varying degrees of auriculoventricular block (first and second degree A-V block) due to digitalis toxicity appeared.

Repeated urinalyses showed essentially the same findings. Blood urea fluctuated between 165 mg. per cent on November 18, to 51 mg. per cent on November 27. Creatinine in the blood varied in the same direction. These changes closely paralleled the volume of urine output, which remained between 300 to 500 c.c. in 24 hours.

On November 29, Arfonad*, administered by continuous intravenous drip, was started in an attempt to control his blood pressure level.[7] The dose required to maintain the blood pressure level at approximately 220 mm. Hg systolic to 115 mm. Hg diastolic was remarkably large. During the first 4 days, 500 to 725 mg. of Arfonad was dissolved in 500 c.c. of 5 per cent dextrose in water and administered by continuous intravenous drip at the rate of 2.5 to 4 mg. of Arfonad per minute (40 to 60 drops per minute). After the fifth day the dose required was 1 to 2 mg. of Arfonad per minute. During the treatment with Arfonad, pulmonary râles progressively disappeared and breathing returned to near normal levels. Chest x-rays showed clear lung fields (Fig. 1,*B*). Re-evaluation of the case at this time led to a tentative diagnosis of occlusion of the renal arteries,

*Supplied by Hoffmann-La Roche, Inc.

with renal ischemia as a possible cause of hypertension and reduced diuresis. Aortography* confirmed the diagnosis (Figs. 2 and 3). On December 11, the patient was operated.† The abdominal aorta was exposed through a thoracic and abdominal incision, clamped, and entered.



A.

B.

Fig. 1.—*A*, Chest film showing acute pulmonary edema at the time the patient entered the hospital. *B*, After one week of continuous intravenous treatment with Arfonad, the lung fields are clear and signs of edema have disappeared.

A nonadherent thrombus which extended from 2 cm. above both renal arteries to the terminal aorta was easily extracted. The terminal aorta, and both iliac and femoral arteries showed a chronic adherent thrombotic occlusion, but no attempt was made to correct it. Palpation of both renal arteries and kidneys showed that they were grossly normal. The section was clearly evident in the specimen where the thrombus protruded slightly into both renal arteries. Exploration of the stomach showed a muscular hypertrophy of the pylorus, but no correction was at-

*Aortography was performed by Dr. J. McCook.

†Operation was performed by Dr. Antonio Rodriguez Diaz.

tempted. During the first 6 hours after operation the blood pressure level returned to normal (150 mm. Hg systolic and 70 mm. Hg diastolic), and diuresis increased markedly. The patient voided 4 liters during the first 6 hours (Fig. 4).

During the first 10 postoperative days the blood pressure level was very unstable, fluctuating between 135 to 230 mm. Hg systolic and 70 to 100 mm. Hg diastolic. On the second postoperative day, during a hypertensive crisis, Arfonad was again administered in the same manner as before at a rate of 1 mg. per minute. After 5 mg. of the drug had entered the vein, the blood pressure level fell to 100 mm. Hg systolic and 40 mm. Hg diastolic, and Arfonad was quickly discontinued. This rapid and intense response to the drug was in contrast to that obtained before the

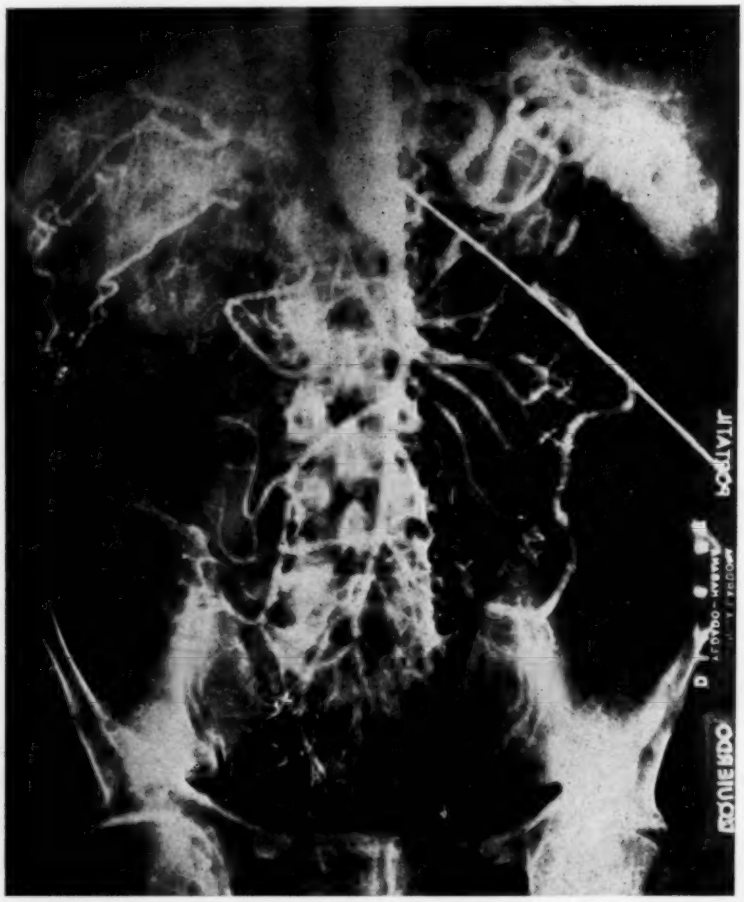


Fig. 2.—Aortography showing occlusion of the abdominal aorta above the level of the renal arteries. The inferior mesenteric artery is enlarged and provides a profuse collateral circulation. No evidence of renal arteries can be detected in this film.

operation. The postoperative course was difficult because of the changes in blood pressure and a persistent intestinal paresis, which was finally controlled with gastric suction and cholinergic drugs. Electrolyte balance was performed during this period, and the necessary electrolyte replacements given by vein. The blood pressure level stablized progressively and ranged with little variations between 140 and 160 mm. Hg systolic and 70 and 95 mm. Hg diastolic.

The patient was dismissed from the hospital on the twentieth postoperative day, with a maintenance treatment of anticoagulants, chlorothiazide and digitalis (which were started on the third postoperative day). Laboratory tests at the time of dismissal showed a blood count of 4.05

million red cells, 9,500 white cells, 71 per cent neutrophils, 3 per cent eosinophils, 20 per cent lymphocytes, and 6 per cent monocytes. Blood urea was 31 mg. per cent, and the sedimentation rate was 39 mm. the first hour and 84 mm. the second hour. Urinalysis showed a slight trace of albumin, 10 white cells, 1 red cell, and no casts.

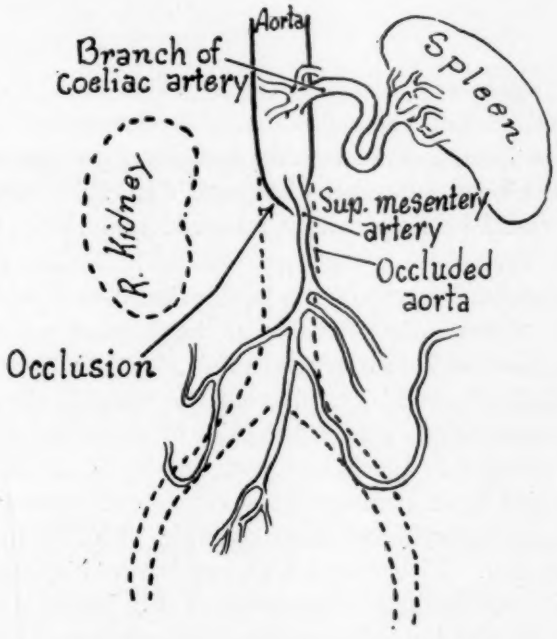


Fig. 3.—Schema of aortography in Fig. 2.

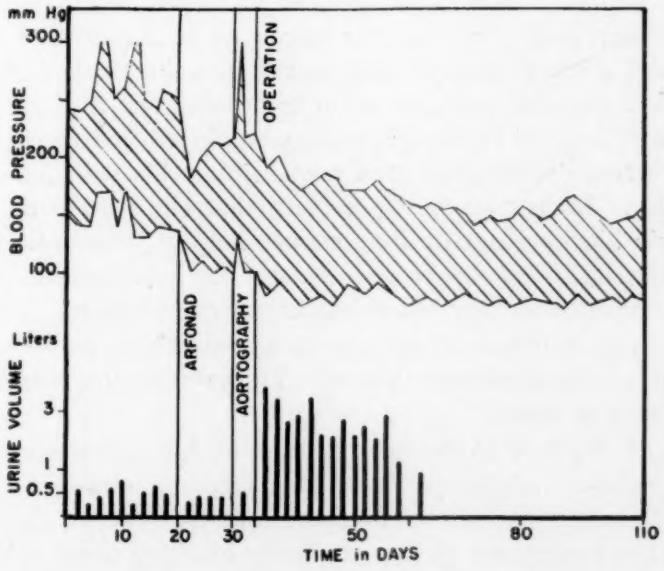


Fig. 4.—Semischematic representation of this case showing significant findings. Blood pressure levels represent the average of those taken during the day.

The patient has remained under observation during the past 5 months, and has gained 20 pounds since dismissal from the hospital; he feels well and is active. Examination of the eye grounds 4 months after surgery showed disappearance of exudates and hemorrhages; there is a slight narrowing of retinal arteries and minimal arteriovenous compression (Wegener Grade 1). His blood pressure level has ranged from 140 to 160 mm. Hg systolic and 85 to 105 mm. Hg diastolic.

DISCUSSION

Since the first account of experimental hypertension secondary to renal ischemia, in dogs,[1] a great deal of interest has developed in this form of hypertension. There have been a number of reports[2,3] in which the underlying cause of renal ischemia could be successfully removed and the patient permanently cured.

The present observation appears to be another case in which renal ischemia due to incomplete thrombotic occlusion of both renal arteries determined a sustained hypertension with paroxysmal crisis, leading to acute heart failure, which was successfully "cured" by relieving the thrombotic obstruction. It is interesting to comment briefly on the behavior of the blood pressure level under the effect of the ganglionic blocking agent employed in this case (Arfonad). Page and McCubbin[4] have demonstrated consistent pressor responses to the administration of tetra-ethylammonium chloride (TECA) in the experimental renal hypertensive dog. Fisher and Corcoran[5] have reported similar results in a patient having abdominal coarctation of the aorta with resultant renal hypertension. Brust and Ferris[6] have used the response of the blood pressure to the administration of TECA as a means of clarifying which mechanisms support or inhibit the blood pressure level. On the basis of pressor or depressor responses these authors have designated the control of vascular tone as being primarily neurogenic, primarily humoral, or an interaction of both mechanisms.

In the present case, Arfonad was employed as a means of controlling the dangerously high level of blood pressure and suppressing the hypertensive crisis.[7,8] No pressor effect was observed during the treatment, but the lack of a significant drop in pressure, in spite of the large doses employed, led to the suspicion that probably a humoral mechanism was responsible; this was demonstrated later by aortography. Recent studies[9] postulate that the testing of blood pressure with ganglionic blocking agents may supply helpful information from at least two standpoints: (1) It helps to characterize the hypertension as being indeed of renal origin when a kidney lesion has been demonstrated. (2) A pressor response or no drop in blood pressure to ganglionic block may suggest potential reversibility of the hypertensive process. The present observation is in general agreement with this work.

The lack of response to the average dose of Arfonad was consistent with a humoral mechanism of hypertension. The response observed after operation corroborates this interpretation. The fact that the level of the blood pressure fell slightly when large doses of the ganglionic blocking agent were administered is consistent with the interpretation that the hypertension was predominantly reversible. Observations for 6 months after operation seem to confirm that the

paroxysmal crises of hypertension have been permanently cured, and that the patient remains with a mild benign hypertension. Blood pressure levels are near the normal range. Mild hypertension probably was the underlying disease before development of the subacute bilateral renal ischemia.

SUMMARY

Presented is a case of severe hypertension with frequent paroxysmal crises of hypertension and acute pulmonary edema on the basis of bilateral renal ischemia. Continuous intravenous treatment with large doses of Arfonad abolished the paroxysmal crisis and the pulmonary edema. Some unusual features of the response of the blood pressure to this ganglionic blocking agent are discussed and considered useful in the diagnosis of hypertension due to renal ischemia. Removal of the offending aortic thrombus which extended from above the entrance of both renal arteries to the terminal aorta was followed by a reduction in the level of the blood pressure, profuse diuresis, and "cure."

The authors wish to thank Mr. Walter Filli and Mr. Conrado Garcia from Hoffmann-La Roche, Inc., for the generous supply of Arfonad used in this case.

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A Simple Indexing System for Electrocardiograms

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In most hospitals and even in some private offices, electrocardiograms are used not only for purely diagnostic considerations but also for the purpose of teaching and research. In order to make electrocardiograms with specific patterns or types of arrhythmia available at short notice when they are needed for these purposes, several cross-reference and indexing systems have been developed. In the system recommended by Barker[1] each pattern or type of arrhythmia is assigned a combination of letters and numbers, and a small index card bearing the serial number of the electrocardiogram is prepared for each pattern shown by this particular curve. The decimal systems of classification developed by Pick and Katz[2] or by the author[3] can be used also. However, the cost and bulk of such a filing system, as well as the time necessary to put it into effect, can be considerable. Furthermore, an important disadvantage is that no further information is available in the index cards concerning other electrocardiographic and clinical findings accompanying the desired pattern in each case, so that the original electrocardiograms and case histories must be located and studied in order to determine whether they can be used or not.

The disadvantages outlined above are not present in the marginal punch-hole card system, which has been used extensively for other medical data,[4] and which has been recently adopted for use in electrocardiography.[5] In this system, clinical information about the patient is contained in the center of a 5 by 8-inch, or larger, card, while the edges of the card contain up to 200 numbered holes, each corresponding to a pattern or other piece of information. When a particular item occurs on a card, the hole corresponding to this item is enlarged toward the edge by means of a special punch. When all cards bearing this item are desired, the cards are put on a special sorting tray, a long steel rod is inserted through the corresponding hole, and all cards except those in which this item has been punched are lifted out. Aside from the high cost of the cards and sorting equipment, the

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*This work was done during the tenure of an Established Investigatorship of the American Heart Association.

system has the disadvantage that all the cards must be taken out of the files for sorting, and that the cards with the desired item must be refiled in the proper sequence even if they are not used.

The system developed by the author was designed to avoid the disadvantages mentioned above and to minimize the time necessary to index the findings and to locate the needed topics. The request slips for electrocardiograms are printed on 5 by 8-inch cards which contain spaces for detailed clinical information about the patient, to be filled out by the person requesting the test or by the technician. If the name-plate system is used by the hospital, the name of the patient and some of this information is printed automatically on the request card as well as on the attached interpretation sheet and charge slip. When the interpretation is written, a carbon copy is made on the back of the request card. These request cards are filed in the electrocardiographic laboratory alphabetically according to the name of the patient, while the mounted electrocardiograms are filed in the record office together with the charts. When the interpretation is made, care is taken to describe the most important electrocardiographic findings in addition to stating the clinically important conclusions. This facilitates the understanding of the electrocardiograms by medical students, interns, and doctors with little electrocardiographic experience, and at the same time makes approximate reconstruction of the electrocardiogram possible should the original tracing become lost or damaged.[6] A detailed description also makes it possible for a relatively untrained person to carry out the cross indexing by placing a marker on the upper edge of the card when a certain electrocardiographic pattern or diagnosis appears in the description or interpretation. The upper edge of the card is subdivided into 32 numbered spaces, each ¼ inch wide. A ¼-inch wide strip of colored adhesive tape (the "Mystik" brand proved most satisfactory) is attached to the corresponding space on the card, protruding ¼ inch beyond this edge. During this process, the strip is folded over with its adhesive surface facing inside and this surface attached to both the front and back surfaces of the card. When the cards are filed, the strips of tape are well visible from above, and can be identified easily by holding a card, with the patterns typed in their respective locations, above the open filing drawer. The entire clinical and electrocardiographic information concerning each electrocardiogram can be read from the card without taking it out of the drawer; if the electrocardiogram in question does not correspond to the desired pattern, the card can be left in the drawer and the next card examined.

As mentioned above, each card has room for 32 markers, corresponding to 32 items. By using tapes of different colors the total number of items which can be cross-indexed is made practically unlimited. The author uses blue tape for changes in the form of the electrocardiogram, red tape for different types of arrhythmias, and yellow tape for special tests or measurements taken for research purposes, but other designations can be used if required. The following are the items most frequently used by us. *Blue:* 1. P pulmonale. 2. P Mitrale. 3. Other P wave patterns. 4. Low voltage. 5. High voltage. 6. Left ventricular hypertrophy. 7. Left ventricular strain. 8. Left bundle branch block. 9. Peri-infarction block. 10. Right ventricular hypertrophy. 11. Right bundle branch

block. 12. Right bundle branch block, atypical or focal. 13. Acute cor pulmonale and right ventricular strain (pulmonary embolism). 14. Children and juvenile T wave pattern. 15. Anterior myocardial infarction. 16. Lateral infarction or injury. 17. Posterior, inferior, diaphragmatic infarction. 18. Subendocardial infarction or injury. 19. Coronary insufficiency. 20. Myocardial ischemia. 21. Pericarditis or pericardial irritation. 22. S-T elevation, normal. 23. Tall T waves, normal. 24. Tall U waves. 25. Negative, diphasic or notched U waves. 26. Digitalis. 27. Quinidine. 28. Procaine (Pronestyl). 29. Hypocalcemia. 30. Hypercalcemia. 31. Hypopotassemia. 32. Hyperpotassemia. *Red:* 1. Sinus arrhythmia, marked. 2. Sinus tachycardia. 3. Sinus extrasystoles. 4. Sinus bradycardia. 5. Sinus arrest. 6. Sino-atrial block. 7. Atrial extrasystoles and escape rhythms. 8. Atrial parasystole. 9. Wandering atrial pacemaker. 10. Atrial paroxysmal tachycardia with block. 11. Atrial tachycardia. 12. Coronary sinus rhythm. 13. Atrial flutter. 14. Atrial fibrillation. 15. A-V nodal extrasystoles or escape beats. 16 A-V nodal tachycardia. 17. Supraventricular rhythms. 18. A-V block, incomplete (long P-R). 19. A-V block, complete. 20. A-V block, partial. 21. A-V block, Wenckebach type. 22. A-V dissociation, isorhythmic. 23. Ventricular extrasystoles and escape rhythms. 24. Ventricular parasystole. 25. Ventricular paroxysmal tachycardia. 26. Ventricular flutter and fibrillation. 27. Reciprocal rhythms. 28. Pre-excitation (Wolff-Parkinson-White Syndrome).

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Review

Pathologic Study of Persistent Common Atrioventricular Canal

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A decade has passed since the first review on the subject of persistent common atrioventricular canal from this institution.[1] In the intervening years sufficient cases with necropsy study have been added to our pathologic series and to the literature to warrant a second review.

This is a report of 28 cases of persistent common atrioventricular canal (Table I)—including the 5 previously reported by Rogers and Edwards,[1] as well as a sixth case subsequently reported by Rogers and Rudolph[2]—and a classification of the types of this lesion, together with a brief review of the literature. In the previous report dealing with the pathologic findings, two types of this lesion, namely, the complete and the partial forms, were described.[1] Distinguished in this report is another type referred to as the intermediate form (elsewhere called "transitional"[4]).

The basic material for this study consisted of 27 hearts examined at the Mayo Clinic, and photographs of a twenty-eighth specimen from a subject who had been studied clinically here. The malformations were of the complete type in 16 cases, of the partial type in 5, and of the intermediate type in 7. The clinical and hemodynamic findings associated with this cardiac anomaly are to be presented in a separate report.[5]

REVIEW OF PUBLISHED REPORTS

In the review of 1948, Rogers and Edwards[1] assembled published accounts of 50 necropsy cases, and added reports of 5 more (now among the 28 primary

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cases of this study). Further search of publications has revealed 30 cases studied at necropsy reported subsequent to the last review, and 1 other such case reported (Uhley[6]) prior to but not included in that review (Table II).[6-21] (Not included among these 31 is the case reported by Rogers and Rudolph,[2] from which the specimen was available for direct examination in our study.)

Cases were found which had been misinterpreted either in reviews or in the original report and needed reclassification. Like the case of Tinney and Barnes,[3] to which it is almost identical, Uhley's case[6] was reported as Lutembacher's syndrome. The published photograph shows the cleft anterior mitral valve leaflet and the crescent-shaped (arch-shaped) low defect of the atrial septum. The case of Askey and Kahler,[9] another example of persistent common atrioventricular canal in a man of mature years, also was reported as Lutembacher's syndrome. The photographs of the heart reveal the cleft anterior mitral valve leaflet and the deformed septal leaflet of the tricuspid valve. On restudy, the case of a 55-day-old Mongoloid reported by Albores[22] was found to include an atrial septal defect associated with a separate ventricular septal defect, and not to be persistent common atrioventricular canal. Case 3 of Blount and associates[21] was the only case among the 5 which they reported that had findings on physical examination, electrocardiography, and fluoroscopy different from those in their other cases of persistent common atrioventricular canal. The published photograph of the left atrium and left ventricle shows an interatrial communication above the posterior medial commissure of the mitral valve which is more posterior than the defect of the atrial septum seen in cases of persistent common atrioventricular canal. The lack of anatomic abnormalities of the atrioventricular valves is made clear; this case is excluded from our tabulation.

TERMINOLOGY AND CLASSIFICATION

In a recent review of this anomaly the term "endocardial cushion defect," introduced by Watkins and Gross,[23] was fully elaborated by Campbell and Missen.[24] This term represents well the pathogenesis of the lesion under study. It does not, however, satisfactorily distinguish this lesion from other cardiac anomalies resulting from malformation of the endocardial cushions.

Another suggestion is "persistent ostium primum atrial septal defect." Regarding the identifiable structures of the atrial septum, there may be deficiencies or absence of the lower limbus of the fossa ovalis in all types of persistent common atrioventricular canal. The limbi of the fossa ovalis are derived from the septum secundum; therefore, a defect of the lower limbus in association with a defect of the lower part of the atrial septum (ostium primum) is a deficiency of the septum primum and of the septum secundum alike. It would be erroneous to refer to this interatrial communication as simply a defect of the septum primum.

Furthermore, in our experience, the persistent ostium primum defect has been associated invariably with other anomalies of the atrioventricular valves.*

*Since the time of preparation of this paper, Dr. Luis Becu, of Buenos Aires, has submitted to one of us (J. E. E.) illustrations of a heart having the atrial and ventricular septal defects characteristic of this malformation, but with the valves intact.

TABLE I. DATA FROM 28 CASES OF PERSISTENT COMMON ATRIOVENTRICULAR CANAL

CASE	SEX	AGE AT DEATH	HEART WEIGHT (GM.)	THICKNESS OF WALL (CM.)		SIZE OF LOW DEFECT OF ATRIAL SEPTUM (CM.)	LOWER LIMBUS	PATENT FORAMEN OVALE	COMMUNICATION BENEATH A-V VALVE	ASSOCIATED DEFECTS	CAUSE OF DEATH
				RV	LV						
Complete											
1.	M	0	25	0.3	0.2	<1 x <1	+	+	+	Patent ductus arteriosus	Stillbirth
2.[a]	M	0	—	0.3	0.3	0.4 x 0.4	0	+	+	Patent ductus arteriosus, right aortic arch, anomalous origin of left subclavian artery, left superior vena cava	Stillbirth
3.	F	0	—	0.4	0.5	0.7 x 1.0	0	+	+	Patent ductus arteriosus	Stillbirth
4.[a]	F	3 days	—	0.4	0.4	<1 x <1	0	+	+	Patent ductus arteriosus, bicuspid pulmonary and aortic valves	—
5.	F	16 days	—	0.4	0.3	1 x 1	0	0	0	None	Postoperative (for congenital atresia of esophagus)
6.[b]	F	2½ mo.	—	0.3	0.6	1.8 x 0.9	0	+	+	None	Bronchopneumonia
7.[b]	F	5 mo.	41	0.7	0.8	2 x 2	+	0	+	None	Bronchopneumonia
8.[b]	M	5 mo.	54	0.5	0.5	1 x 1	+	0	+	None	Bronchopneumonia
9.	F	7 mo.	—	0.9	1.0	2.2 x 1.2	+	+	+	None	Congestive heart failure
10.	M	10 mo.	60	0.9	0.7	1.7 x 1.2	0	+	+	None	Congestive heart failure
11.	F	12 mo.	—	0.4	0.5	1.3 x 1.3	+	+	+	Patent ductus arteriosus	Respiratory infection
12.	M	13 mo.	—	0.6	0.5	2 x 2	0	0	0	None	Postoperative

TABLE I. DATA FROM 28 CASES OF PERSISTENT COMMON ATRIOVENTRICULAR CANAL—CONT'D.

CASE	SEX	AGE AT DEATH	HEART WEIGHT (GM.)	THICKNESS OF WALL (CM.)		SIZE OF LOW DEFECT OF ATRIAL SEPTUM (CM.)	LOWER LIMBUS	PATENT FORAMEN OVALE	COMMUNICATION BENEATH A-V VALVE	ASSOCIATED DEFECTS	CAUSE OF DEATH
				RV	LV						
Complete											
13.[a,c]	M	16 mo.	—	1.1	0.9	3.6 x 1.8	0	+	+	None	Congestive heart failure
14.	F	2½ yr.	—	0.9	1.0	3 x 2.5	+	0	+	Double mitral valve	Postoperative
15.	M	13 yr.	530	0.6	1.0	5.3 x 4	+	+	+	Double mitral valve, bicuspid pulmonary valve, coronary sinus connected to left atrium, atresic right atrial ostium of coronary sinus	Postoperative
16.[d]	M	22 yr.	—	—	—	—	0	0	—	None	Congestive heart failure
Intermediate											
17.	F	12 days	32	0.3	0.3	1.5 x 1.5	+	0	+	Patent ductus arteriosus, double mitral valve, coarctation of aorta proximal to ductus, anomalous origin of right subclavian artery	Pulmonary edema
18.	F	17 days	22	0.4	0.3	2.0 x 1.5	0	0	+	None	Congestion of lungs
19.	M	1 mo.	—	0.5	0.6	0.6 x 0.6	0	0	0	None	Congestive heart failure
20.	M	6 mo.	130	0.7	0.4	2.0 x 1.5	+	+	0	Double mitral valve	Postoperative
21.	F	14 mo.	—	—	—	1 x 1.5	0	0	+	Double mitral valve	Postoperative

22.	F	26 mo.	—	0.6	0.8	2 x 3.0	+	0	+	Coronary sinus connected to left atrium, atresic right atrial ostium of coronary sinus	Postoperative
23.	M	3½ yr.	240	0.4	1.1	2.0 x 1.5	+	0	0	None	Cerebral anoxia, pulmonary congestion
						Partial					
24.[b]	M	5 mo.	88	0.5	0.6	1.6 x 1.4	+	+	0	None	Bronchopneumonia
25.	M	2½ yr.	—	0.5	0.5	2.5 x 2.5	0	0	0	None	Congestive heart failure
26.	M	5 yr.	250	1.0	1.2	2.0 x 1.6	+	0	0	Aortic coarctation	Operative
27.	F	27 yr.	300	0.6	1.8	2.5 x 1.8	+	0	+	None	Operative
28.[b,e]	M	37 yr.	575	1.2	0.9	4.0 x 3.0	+	0	0	Subacute bacterial endocarditis	Congestive heart failure

+ Present.
0 Absent.
– Data not available.
RV = Right ventricle. LV = Left ventricle. A-V = Atrioventricular.
a = Gross specimens from outside sources submitted to Section of Pathologic Anatomy.
b = Reported by Rogers and Edwards.[1]
c = Reported by Rogers and Rudolph.[2]
d = Only photographs submitted to Section of Pathologic Anatomy.
e = Reported by Tinney and Barnes.[3]

TABLE II. DATA FROM 31 NECROPSY CASES REPORTED SINCE EARLIER REPORT*

REPORT	AGE	SEX	MONGOLISM	CYANOSIS	PICTURE	ASSOCIATED DEFECT	CAUSE OF DEATH
Uhley[6]	60 yr.	M	0	+	+	Rheumatic mitral valvular thickening	Congestive heart failure
Ingalls[7]	26 days	−	+	−	0		
	8 mo.	−	+	−	0		
	48 mo.	−	+	−	+		
	16 mo.	−	+	−	0		
Wurtz and Powell[8]	9 mo.	M	+	−	+	Dextroposition of aorta	Pneumonia, cardiac failure
Askey and Kahler[9]	72 yr.	M	0	+	+	Calcified mitral stenosis	Uremia
Cahen, et al.[10]	49 yr.	M	−	−	+		
	21 yr.	F	−	−	+	Subacute bacterial endocarditis	Pulmonary embolus, congestive heart failure
Potter[11]	15 days	−	+	−	+		
Curtin[12]	58 yr.	F	0	−	+		Congestive heart failure
Hambach[13]	6 mo.	F	+	−	+	Patent foramen ovale	Pneumonia, myocarditis
	9 days	M	+	+	0	Patent foramen ovale, patent ductus arteriosus, corrected transposition, hypoplasia of aorta	Bronchopneumonia, intracranial hemorrhage
	1 day	F	+	−	0	Patent foramen ovale, complete transposition, patent ductus arteriosus	Atelectasis

Strauss[14]	3 days	—	0	−	0	Retroesophageal right subclavian artery	
	37 days	—	+	−	+		
	6 mo.	M	+	−	+		Congestive heart failure
	2½ mo.	—	+	−	0	Anomalous origin of retroesophageal right subclavian artery	
	1 yr.	—	+	−	0		
Rossi[15]	5½ mo.	F	−	−	+		
	6 mo.	M	−	−	+		
Metianu, et al.[16]	2½ yr.	F	−	+	+		
Kjellberg, et al.[17]	4½ yr.	F	0	+	+		
	1 yr.	F	0	+	0		
	2 mo.	M	+	+	+		
Lewis, et al.[18]	4 yr.	—	−	−	0		Postoperative
	7 mo.	—	−	−	0		Postoperative
Lillehei, et al.[19]	5 mo.	—	−	−	0		
Behnke and Beamer[20]	26 yr.	M	0	+	0	Bicuspid aortic valve	
Blount, et al.[21]	4 yr.	M	0	−	+		Postoperative
	27 mo.	M	0	−	0		Postoperative

*Cases reported from 1846 to 1946 were tabulated by Rogers and Edwards, except for that of Uhley (1942)[6] which therefore is included here.
+ Present.
0 Absent.
− Data not available.

Hence, the term "ostium primum defect" indicates only part of a complex malformation of the atrioventricular region. In order to include the various features of the malformation under one term, we prefer to use "persistent common atrioventricular canal," with further subdivision into three types: complete, partial, and intermediate.[4]

Complete Form.—In the complete form of this malformation there is anatomic evidence of lack of fusion of the two atrioventricular endocardial cushions with each other and with the atrial and ventricular septal complexes. This single developmental failure is manifested by the following features: (1) a continuous cleft through both the anterior mitral leaflet and the septal tricuspid leaflet, (2) an interventricular communication through a subvalvular space above the ventricular septum, and (3) an interatrial communication through a low-positioned defect of the atrial septum with an arch-shaped upper border.

Visible from the atria is a single valve common to both sides of the heart, with a large anterior leaflet and somewhat smaller posterior leaflet. These are derived from the unfused ventral and dorsal endocardial cushions, respectively. The opening between the free edges of the anterior and posterior leaflets reaches from the normal site of the mitral orifice to that of the tricuspid, thus amounting to a continuity of the clefts in the mitral and tricuspid valve leaflets. The superior edge of the ventricular septum stands free.

Partial Form.—In the partial type of persistent common atrioventricular canal the heart has developed further toward the normal condition than in the complete form, but the basic deficiencies in development are similar. A cleft in the anterior leaflet of the mitral valve is anatomic evidence that the dorsal and ventral atrioventricular cushions failed to fuse on the left side. On the right side the endocardial cushions are fused with each other normally. Therefore the tricuspid valve leaflets are normal or nearly so; occasionally there may be some unusual shortening of the septal leaflet, but no true cleft.

The atrial component in the partial type of defect resembles that in the complete form. In the complete form the uninterrupted cleft between what is conventionally called the mitral orifice and the tricuspid orifice is continuous with the lower portion of the atrial component of the malformation. In the partial form the common canal persists on the left side as an extension of the mitral orifice into the cleft of its anterior leaflet, but is obliterated normally in the right side; and the intact septal leaflet of the tricuspid valve forms the lower edge of the atrial septal defect.

In the partial form of common atrioventricular canal there usually is no interventricular communication.

Intermediate Form.—Features of both the complete and the partial forms comprise the intermediate form of persistent common atrioventricular canal. Anatomic evidence suggests that probably minute extensions of the dorsal and ventral atrioventricular cushions fused at their midline, but not sufficiently so on either the right side or the left to obliterate the common atrioventricular cleft completely. Therefore, clefts are present in both the anterior mitral leaflet and the septal tricuspid leaflet, but—in distinction from either of the other forms

discussed—a narrow bridge of valvular tissue in the midline joins the anterior half of each of the two cleft atrioventricular valvular leaflets with their respective posterior halves just above the ventricular septum (Fig. 1). This narrow junction of valvular tissue interrupts the common cleft, which otherwise would run between the leaflets from the mitral orifice to the tricuspid orifice.

The atrial component of the defect is similar to that in the partial and complete varieties, except that a lower edge of the septal defect is formed by the bridge of valvular tissue.

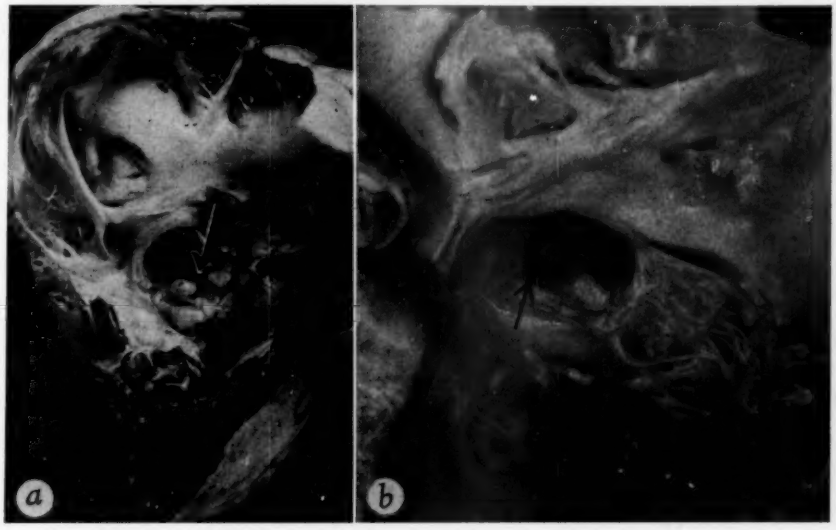

Fig. 1.—Transitional form of persistent common atrioventricular canal. *a*, View from the right, looking into the right atrial and ventricular chambers and at the ventricular septum. Evidence of partial fusion of the endocardial cushions is a narrow bridge of valvular tissue (arrow) joining the anterior and posterior components of the cleft septal tricuspid leaflet over the ventricular septum which borders the arch-shaped atrial septal defect. *b*, View from the left, showing the cleavage of the anterior mitral valve leaflet and the defect of the atrial septum. The latter is bordered by the valvular tissue (arrow) over the superior edge of the ventricular septum. This small bridge of tissue distinguishes the intermediate (transitional) type from the other two forms of persistent common atrioventricular canal.

The ventricular component of the intermediate type of the malformation is suggestive of those in both the complete and partial forms. Beneath the atrioventricular valve the membranous ventricular septum is defective. Its upper edge curves downward with a broad sweep, extending into the subaortic region. Tissue resembling fused chordae reaches from this edge to the ventricular surface of the septal tricuspid leaflet and the cleft anterior mitral leaflet. From the right side, it is apparent that its insertion is along the posteroinferior aspects of the crista supraventricularis. This tissue similar to fused chordae fills the space ordinarily occupied by the upper part of the membranous septum. It may seal any subvalvular interventricular passage; or openings—interchordal spaces, so to speak—may be present, providing an anatomic and possibly functional interventricular communication.

FINDINGS IN PRIMARY CONGENITAL MALFORMATION

Clefts of Atrioventricular Valvular Leaflets.—The nature and appearance of the clefts of the atrioventricular valvular leaflets have been described sufficiently in the classification just preceding.

Communication Beneath Atrioventricular Valves.—Twenty-seven heart specimens were examined for the presence of interventricular communications beneath the atrioventricular valve. Among 15 hearts with anomalies of the complete type, 13 were found to have communications between the two ventricles beneath either the anterior or posterior leaflet, or both. In the other 2 specimens there were some subvalvular spaces, but of minute size; conceivably, they did not represent significant communication of the ventricles. Four of the 7 heart specimens having the intermediate form of the anomaly, and 1 of the 5 specimens with the partial form, had small interventricular communications beneath the atrioventricular valve.

Defect of Low Atrial Septum.—The dimensions of the arch-shaped defect of the lower part of the atrial septum were measured in all but one specimen. The largest defect measured 5.3 by 4 cm., in a specimen from a 13-year-old child (Case 15), whereas the smallest was 0.4 by 0.4 cm., in a heart from a stillborn fetus (Case 2). In 15 instances the defects measured between 1 by 1 cm. and 2 by 2 cm., inclusive, 7 being larger and 5 smaller.

ASSOCIATED CONGENITAL DEFECTS AND CONDITIONS

Deficiency of Lower Limbus of Fossa Ovalis.—In cases of persistent common atrioventricular canal, evidence of complete development of the septum secundum implies that the septum primum also developed to the full extent; and absence of the lower limbus of the septum secundum suggests that the septum primum also is deficient. Therefore it was of interest to study the specimens with respect to the presence or absence of a lower limbus. Only in 1 of the 5 cases of the partial type was this structure not identified; but it was absent in 9 of the 16 cases of the complete type, and in 3 of the 7 cases of the intermediate type. In the presence of a lower limbus a defect at the fossa ovalis was noted in 1 among 4 specimens in which the malformation was the partial type, in 1 among 3 of the intermediate type, and in 4 among 7 of the complete type. The rather common occurrence of a lower limbus—in 15 of 28 cases—suggests that in some instances the atrial septal tissue had contributed fully, but that the defect in the lower part of the atrial septum might be the result of deficient upward growth of the atrioventricular endocardial cushions. In others, absence of the lower limbus may represent deficiency in both the upward growth of the cushions and the downward growth of septum primum and septum secundum.

Patent Foramen Ovale.—A septal defect in the region of the fossa ovalis is the most frequently associated defect seen in cases of persistent common atrioventricular canal. Twelve of the 28 specimens in this anatomic study were found to have atrial septal defects, of which 2 were fenestrations. The defect was much more frequent in cases of the complete form, being present in 10 (62 per cent) of the 16 specimens, in contrast to being found in only 1 specimen each of

the intermediate and partial forms. A probe-patent but valvular-competent type of patent foramen ovale was found in 12 additional cases, and in only 4 other cases was the foramen ovale completely closed anatomically.

Usually the defect of the foramen ovale is smaller than the adjacent lower defect; but unlike the other, which is fairly uniform in size, the defect of the foramen ovale varies considerably in extent.

In the literature the condition of the atrial septum was mentioned in reports of 42 cases, among which 27 had an atrial septal defect at the fossa ovalis separate from the low crescent-shaped defect. Fenestrations of the fossa ovalis were noted in 4 of the 27 cases. Thus, in the literature and the present series the total incidence of associated significant atrial septal defects of varying sizes (but not fenestrations) with persistent common atrioventricular canal is about 45 per cent.

Patent Ductus Arteriosus.—The second most frequently associated communication between the two circulations was patent ductus arteriosus. It was present in 6 cases in our series: in 5 of the complete type (Cases 1-4, and 11) and in 1 of the intermediate type (Case 17).

In the normal newborn infant the lumen of the ductus arteriosus remains anatomically patent for varying periods up to 6 or 8 weeks after birth[25]; therefore, the significance of patency of the ductus arteriosus in any infant less than 2 months of age may be questioned. Five of the 6 cases of patent ductus arteriosus in our study came within this age limit. Three of the subjects were stillborn and 2 were less than 12 days old at death. The sixth subject lived a year, and is the only one considered to have had a significant patent ductus arteriosus.

The literature revealed 7 other instances in which the subjects were less than 4 months old, and only 5 whose ages—4 months, 9½ months, 18 months, 2 years, and 8 years—made the patency significant. The age of a twelfth subject was not known.

Double Mitral Valve.—A fascinating and rare associated cardiac anomaly called "accessory" or "double" mitral valve deserves mention under a separate heading. It consists of two separate mitral orifices, each with valve leaflets attached to chordae tendineae from papillary muscles (Fig. 2). Five instances were examined in our study. In each, the accessory mitral valvular orifice was smaller and was located in the lateral aspect of the posterior leaflet. With its own papillary muscles and chordae tendineae attached to its rim, this second mitral structure conceivably functioned as a competent valve. Three of the 5 instances were among cases of the intermediate type (Cases 17, 20, and 21), and 2 were among those of the complete type (Cases 14 and 15).

The developmental basis of this anomaly was discussed at length by Wimsatt and Lewis,[26] with the presentation of each coauthor's view. Wimsatt believed that the accessory mitral orifice was not an opening in one of the mitral leaflets, but that it resulted from bisection of the mitral orifice into two distinct orifices. The cause for this supposed bisection of the mitral orifice was given as an abnormal fusion between the anlagen of the medial and lateral mitral leaflets. He assumed that an abnormal bridge of tissue had passed across the left atrioventricular orifice and joined the lateral and medial mitral valvular primordia.

Lewis, in the same article, set the basis for the abnormality at an earlier stage in the development of the heart. He believed that the accessory opening represented persistence of part of the embryonic common atrioventricular canal. This could occur if the left tubercles of the dorsal and ventral endocardial cushions should join before the remainder of the two cushions had joined completely; an opening would be present in the tissue destined to develop into a mitral leaflet. Persistence of this opening would explain the accessory opening.

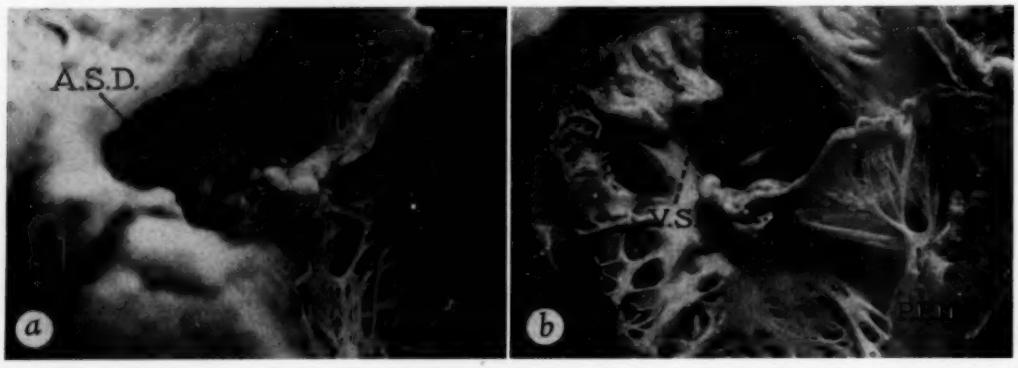

Fig. 2.—Double mitral valve in association with the complete form of persistent common atrioventricular canal. *a*, View from above and slightly left. The accessory (minor) orifice (below arrow) of the mitral valve is located in the lateral part of the posterior mitral leaflet. Numerous chordae can be seen extending downward from the free edges of the accessory orifice. Above and slightly to the left is the arch-shaped interatrial defect (*A.S.D.*). *b*, View from left. The accessory mitral valve and its numerous chordae are seen to form a cone shape with the apex located at the posterior papillary muscle (*P.P.M.*). The septal defect extends into both atrial and ventricular regions, its lower border being the free edge of the ventricular septum (*V.S.*). The anterior mitral leaflet is cleft, as was the septal tricuspid leaflet.

The finding of double mitral valve and persistent common atrioventricular canal in the same heart has been reported recently.[27] In our study this combination was observed in 5 instances. The unusually high incidence of association of these two lesions has not been commented on before.

Other Defects of the Heart and Great Vessels.—In addition to patent foramen ovale, patent ductus arteriosus, and double mitral valve, other and rarer defects of the heart and great vessels may be associated in cases having persistent common atrioventricular canal as the major defect. Thirteen such anomalies were found in 6 of our necropsy cases, and included persistent left superior vena cava, atresic right atrial ostium in the coronary sinus with coronary veins connectd-to the left atrium, congenital bicuspid aortic and pulmonary valves, aortic coe arctation, right aortic arch, and anomalous origin of the left subclavian artery (Cases 2, 4, 15, 17, 22, and 26).

From published reports, 12 cases meeting the same criteria were tabulated in the previous review[1]; and 6 have been documented since (Table II).[8,13,14,20]

Thus, among 109 cases of persistent common atrioventricular canal available for count (50 from the literature assembled in the previous review[1] and 31 newly gathered from publications for Table II, with the 28—including 6 previ-

ously reported—studied more directly in this investigation) there are 24 instances of additional cardiac and great-vessel malformations other than patent foramen ovale, patent ductus arteriosus, and double mitral valve.

Mongolism.—The frequent association of Mongolism with persistent common atrioventricular canal has been commented on by previous authors. Taussig[28] stated that "the diagnosis is based on the law of probability. If a Mongolian idiot has a congenital malformation of the heart which superficially resembles ventricular septal defect and there is no cyanosis, the overwhelming probability is that he has a patent atrioventricularis communis. The demonstration of an abnormally low oxygen saturation of the arterial blood clinches the diagnosis."

Of the 6 instances of Mongolism among the 28 cases in this study, cyanosis had been noted in 5. Four of the 6 subjects (Cases 7, 8, 11, and 16) had the complete type of persistent common atrioventricular canal, one (Case 17) had the intermediate type, and another (Case 24) had the partial type.

ASSOCIATED ACQUIRED CONDITIONS

Cardiac Hypertrophy.—It is the rule rather than the exception to see nearly equal thickness of the right and left ventricular walls in newborn and young infants. As growth and development proceed normally, the left ventricular wall becomes thicker than the right; this disproportion is definite by the end of the first month.[29] The adult proportion is attained by about the fourth month, when the left ventricular wall is at least twice the thickness of the right. This normal progression is altered, however, in some persons with congenital heart disease, the extent of alteration depending on the age of the subject and the severity and duration of the functional derangement.

Ventricular hypertrophy: The thicknesses of the ventricular walls of 26 heart specimens were measured and compared. Of 12 specimens from subjects less than 6 months old, 5 had thicker left ventricles, 4 had ventricular walls of equal thickness, and 3 had thicker right ventricles. Among the 14 specimens from subjects who were 6 and more months old, still only 8 had thicker left ventricles, but even in nearly all of these the right ventricular wall was definitely hypertrophied. Thus, right ventricular hypertrophy was a very common finding.

Similar measurements from 14 cases were reported in the literature; among these the thickness of the right ventricular wall was equal to or greater than that of the left ventricular wall in 6. Among the 8 cases with thicker left ventricular walls, the youngest subject was 9½ months old at death.

Ventricular dilatation: In 13 of 26 instances, dilatation of atria or ventricles, or both, was noted. The right-sided chambers were involved in almost all of these; but in the heart from one subject (Case 23) who had had a moderate degree of mitral regurgitation, only the left atrium was dilated. Among subjects more than 3 years old this was the only one with marked left ventricular hypertrophy but without right ventricular hypertrophy. No form of persistent common atrioventricular canal was associated characteristically with dilatation of any specific chamber.

Cardiac weight: Most of the heart specimens with persistent common atrioventricular canal in the Mayo Clinic's collection have been preserved en bloc with the lungs; therefore, heart weights were available in only 13 cases.

Cardiac hypertrophy was found in most. Only 2 were of predicted normal weight.[30,31] Five weighed one and a half to two times the normal, 2 weighed two to three times normal, and 4 weighed more than three times normal; the heaviest (from the 37-year-old subject) weighed 575 grams.

In published reports the weights of 16 other hearts were recorded, of which only 3 were of normal weight. Six of the 16 weighed one and a half to two times normal, and the remaining 7 weighed two to three times normal.

Thus, approximately 17 per cent (5 hearts) of the combined total of 29 weighed hearts from this series and the literature were of normal weight. Four of these 5 hearts were from young infants.

Subacute Bacterial Endocarditis.—Case 28 of this study was reported originally in 1942, by Tinney and Barnes,[3] as an instance of Lutembacher's syndrome in a 37-year-old man. However, re-examination of the heart[1] revealed that this case should be classified as a partial form of persistent common atrioventricular canal complicated by subacute bacterial endocarditis. Large, friable endocardial vegetations characteristic of subacute bacterial endocarditis were deposited on the atrial surface of the cleft anterior mitral valve leaflet. Ante-mortem blood cultures grew green-producing streptococci. No other case in our series included this complication.

Bacterial endocarditis complicating persistent common atrioventricular canal is rather rare. Only 6 such cases have been reported in the literature thus far, 5 (including that of Tinney and Barnes[3]) having been discussed in the previous review.[1] Cahen and co-workers[10] found a 21-year-old woman to have subacute bacterial endocarditis due to hemolytic streptococci, with ulcerations and vegetations involving the persistent ostium primum. Abundant vegetations were found on the valve as well.

Goetsch's explanation of the infrequent occurrence of subacute bacterial endocarditis in persistent common atrioventricular canal was that the patients usually died at an early age, thereby lessening the chance for the development of this complication.[32] This seems plausible, because 4 of the 6 subjects with subacute bacterial endocarditis were 18 or more years old.

SEX, SURVIVAL, AND CAUSES OF DEATH

Common atrioventricular canal shows no predilection for either sex. Fifteen subjects in our series were males and 13 were females.

Early death was common; with instances of stillbirth and postoperative death excluded, 10 subjects died before the age of 1 year, 1 other before the age of 2 years, and 2 others before the age of 4 years. Of 25 subjects who were living at birth, 21 were less than 6 years old at the time of death. Only 2 subjects reached adulthood, the oldest in our study dying at the age of 37 years.

The typical youthfulness of the subjects represented by the heart specimens in our series reflects the seriousness of the lesion under study. Especially, the

ages represented by the heart specimens with the complete and intermediate types of the anomaly emphasize the severity of these malformations as compared to that of the partial form. Cases of postoperative death excluded, 14 of the 16 subjects with complete and intermediate types died before reaching the age of 2 years; but only 1 subject with the partial form died before his second birthday.

With operative and postoperative deaths and stillbirths excluded, the most common cause of death was congestive heart failure, which accounted for 7 cases. Infection of the respiratory tract—bronchopneumonia—was the second most common cause; implicated in 4 cases, it may have been a complication of pulmonary edema. Only one death—that of the oldest subject—was attributed to subacute bacterial endocarditis with congestive heart failure.

SUMMARY

Persistent common atrioventricular canal is one of the forms of congenital heart disease which stems from the failure of fusion of the endocardial cushions to each other in the embryonic stage. This deficiency in its *complete* form shows a common cleft in the anterior mitral and septal tricuspid valve leaflets and defects of the intracardiac septum above and below, allowing communication among all four chambers of the heart. The superior edge of the ventricular septum stands free. In the least deficient form, referred to as *partial*, fusion of the endocardial cushions is incomplete on the left side only, resulting in a normal septal tricuspid leaflet and a cleft anterior mitral leaflet. There is a pattern which may be called *intermediate* between the complete and partial forms, in which the only evidence of fusion of the endocardial cushions is a small bridge of valvular tissue seen on the superior aspect of the ventricular septum. Common to all three types of persistent common atrioventricular canal is persistence of the ostium primum, which probably is due, at least in part, to failure in the upward growth of the endocardial cushions.

The pathologic data compiled are based on 28 cases of persistent common atrioventricular canal, of which 16 represented the complete, 7 the intermediate, and 5 the partial type.

Subvalvular spaces allowing free interventricular communication were present in 13 of the 15 hearts with the complete form, in 4 of the 7 with the intermediate form, and in 1 of the 5 with the partial form.

The lower limbus of the fossa ovalis was deficient in 13 of the 28 specimens. Nine of these defects were in hearts with the complete form of the malformation, 3 were associated with the intermediate form, and 1 with the partial form.

Cardiac enlargement, including right ventricular hypertrophy, was common. In several hearts biventricular hypertrophy was evident.

Not uncommonly, one or more associated cardiac defects were seen in the specimens studied. Atrial septal defect was noted in 12 specimens, double mitral orifice in 5, and miscellaneous types of defects, including a case of significant patent ductus arteriosus, in 7 others.

Among a total of 109 cases of persistent common atrioventricular canal examined or documented for tabulation are 24 instances with additional cardiac

or great-vessel malformations other than patent foramen ovale and patent ductus arteriosus.

Six examples of subacute bacterial endocarditis complicating this lesion have been documented thus far.

The rare anomaly of double mitral valve was observed in 5 of the 28 hearts with persistent common atrioventricular canal. The frequent association of these two lesions has not been commented on before.

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Book Reviews

LEHRBUCH DER ROENTGENOLOGISCHEN DIFFERENTIALDIAGNOSTIK. BAND I. ERKRANKUNGEN DER BRUSTORGANE. (Textbook of Roentgenological Differential Diagnosis. Vol. I. Diseases of the Chest). By Werner Teschendorf, Ed. 4, Stuttgart, 1958, Georg Thieme, 1,183 pages, 1,138 illustrations. (New York, 1958, Intercontinental Medical Book Corp.)

This is the fourth edition of the first volume of a two-volume *Textbook of Roentgenological Differential Diagnosis.* It deals with the Diseases of the Chest. The second volume, which was published in its third edition, in 1954, dealt with the Diseases of the Abdomen.

The author, who was a pupil of the late Prof. Matthes, of Koenigsberg, dedicated this textbook to the memory of his late teacher, whose textbook *The Differential Diagnosis of the Diseases in Internal Medicine* has become a classic in European medical literature.

The volume under present review consists of five major sections. In the first 637 pages the author deals with the diseases of the lungs, pleura, and mediastinum. The techniques of routine and selective bronchography and of the selective angiography of the pulmonary artery are discussed at length and are well illustrated. A long chapter is devoted to the differential diagnosis of the vascular pattern of the lung, with some emphasis on photofluorographic techniques. A separate chapter deals with the hilar shadow. The value of tomography and of kymography in the study of the diseases of the chest is well reported.

Almost 400 pages of this textbook are devoted to the diseases of the heart and aorta. The author of that section is Priv. Doz. Thurn, of Bonn, who utilized for his section of this book the large material of the University Clinic of Prof. Martini, in Bonn, and the vast cineradiographic data on congenital and acquired cardiac abnormalities of Prof. Janker and the surgical material of Prof. Derra. All present-day methods of cardiac investigation are reviewed; roentgenkymography, electrokymography, cardiac catheterization, angiocardiography, and retrograde aortography and cineradiography are discussed from the point of view of their respective indication.

The methods of cardiac measurement, the hemodynamics of the heart and of the great vessels, the significance of the extracardiac factors in determining the position, size, and shape of the heart, the acquired and congenital diseases of the heart, the anomalies of the great vessels, the diseases of the coronary arteries, the diseases of the myocardium and of the pericardium, the traumatic conditions of the heart, the tumors of the myocardium, and the diseases of the aorta are all thoroughly reviewed and illustrated.

The last two chapters are devoted to the diseases of the esophagus and the visible abnormalities of the diaphragm and their roentgenologic differential diagnosis.

This textbook has 1,138 illustrations on 1,183 pages. There are brief "headlines" on the side of each page in a space left for this purpose on the outer side of the page. This permits a quick review of the subject on a given page, e.g., the heart and the measurements of the human body, isolated enlargement of the left auricle, insufficiency of the heart muscle, dilatation with hypertrophy, etc. The references are placed at the bottom of each page and are brought up to 1957. The index is thoroughly compiled and accurate.

The importance of standard diagnostic procedures is first and foremost stressed in this textbook, notwithstanding the fact that all more elaborate and complicated methods of investigation are described at length.

This book contains a wealth of invaluable information for the internist, cardiologist, surgeon, and radiologist. Its graphic qualities are superb, its illustrations are almost self-explanatory. Its text is lucid and makes very pleasant reading. I only regret that we do not have an English version of it.

D. B.

PHYSIOLOGIE DES HERZENS. By Erich Schütz, Berlin, 1958, Springer Verlag, 570 pages, 229 illustrations.

As stated in the foreword, this is the first comprehensive monograph on the physiology of the heart since R. Tigerstedt's classic *Physiologie des Kreislaufs*. It includes the following chapters: I, Automatic Activity of the Heart; II, Process of Excitation; III, Conduction; IV, Normal and Pathologic Variation of Impulse Duration, Impulse Formation, and Conduction; V, The Indirect Electrocardiogram; VI, Relationship Between Electrical and Mechanical Activity; VII, Valves; VIII, Venous Inflow; IX, Pressure and Volume Curves; X, Heart Sounds; XI, Mechanical Cardiogram; XII, Cardiac Work; XIII, Cardiac Dynamics; XIV, Cardiac Energetics; XV, Coronary Blood Flow; XVI, Cardiac Nerves.

The main purpose of the book was to serve as a bridge between textbook and handbook; therefore, limitation of the material was necessary. Emphasis was placed on experimental facts rather than on "preliminary theories," avoiding supporting one or the other hypothesis in case of controversial situations. Thus, vectorcardiographic theory and "fork-principle" (*Gabelprincip*, based on the author's experiments with forklike divided electrodes) are presented on equal terms as "way of interpretation" of the electrocardiogram (*Betrachtungsweise*). Vector theory is, however, more than that, and some of the supporting fundamental data, such as cancellation experiments, are not mentioned. Of course, an agreement on the arbitrary selection of material is difficult, and criticism on this basis should not detract from the great merits of the book.

It is a scholarly work, and with the advances in all fields of cardiology such a comprehensive book fills an important gap. Electrocardiography and its electrophysiologic basis, which is also the major research field of the author, takes up the major part of the book (Chapters I-VI, pp. 1-236). Much space is devoted also to phonocardiography (pp. 295-348). The more detailed discussion of electrocardiography and heart sounds is justified by their clinical importance, but it is also in these parts that some duplication of existing textbooks occurs. One of the features distinguishing the book is the inclusion of much of the older literature. This book is the culmination of a lifetime of cardiologic research, and is recommended as timely and useful for reference and general orientation.

E. S.

CHEMISTRY AND BIOLOGY OF MUCOPOLYSACCHARIDES (Ciba Foundation Symposium). Edited by G. E. W. Wolstemholme, O.B.E., M.A., B.Ch., and Maeve O'Connor, B.A., Boston, 1958, Little, Brown and Company, 323 pages. Price $8.50.

This volume presents the recent experimental research in the important subgroup of polysaccharides. The book should be of interest to most physicians, particularly those interested in the specialties, as well as to those in other branches of medicine. The volume includes sections on the general chemistry, physical chemical studies, and immunochemical approaches. The relationship of these complexes to various bacteria and the possible significance of this to some clinical entities is discussed in relation to chondroitin sulfate as well as neutral heteropolysaccharides in tissues. Of particular interest to clinicians are the chapters on the pharmacological effects of

polysaccharides in relation to mesenchymal cells—action on resistance to bacterial and viral infection, and the relationship of these substances to allergic phenomena and immune reactions.

As with previous volumes there is much to be gleaned from the open discussion which follows each chapter. There is also a general discussion and summing up at the end. This volume should be a welcome addition to most libraries because of its wide coverage of an interesting and important field.

B. R.

ATLAS UND KURZGEFASSTES LEHRBUCH DER PHONOKARDIOGRAPHIE. By Professor Dr. Med. K. Holldack and Dr. Med. D. Wolf, Stuttgart, 1958, Georg Thieme, 179 pages.

This atlas and short textbook of phonocardiography and related methods of investigations is an expanded second edition. It is a timely contribution to this series of German monographs. It is written in a rather easily readable German, with only occasional long drawn out and involved sentences; however, a knowledge of scientific German is necessary for comprehension of the text. (An English translation of the work would be desirable.) The text has been made quite concise and is illustrated with 160 figures and 197 single halftone reproductions. There are 270 references in the bibliography, and a very good index.

The schematic drawings are excellent; the figures are half photographic and half direct-writing records of simultaneously recorded electrocardiograms, and three or four photocardiograms using different types of frequency filters, usually from only one area on the precordium. The recordings were taken from the one position in which the murmurs and changed heart sounds were best heard. The photographic records are much more satisfactory, since the records taken by the direct writer usually have time marks, originally of yellow or orange, which do not reproduce well enough in the halftones to be read easily. The direct writer is apparently used to emphasize the fact that it is a satisfactory method for all practical purposes and makes unnecessary the purchase of a cathode-ray oscilloscope for monitoring. The authors have reproduced phonocardiograms of sounds and murmurs from every cardiovascular condition, congenital anomalies as well as acquired valvular lesions. They have had great experience, and consider the information that can be obtained from photocardiograms to be of greater practical value than that obtainable from cardiac catheterization, angiocardiography, or electrocardiography. Simultaneous arterial carotid pulse tracings and phlebogram and a jugular venogram are taken with the heart sounds. They dismissed ballistocardiography with the statement that there are too many variables and too many sources of error in the method to make it dependable.

In the first three chapters, the authors describe the physical phases and fundamental theoretical considerations of frequency of filters, possible technical errors and how they are to be avoided. They give practical, meticulous directions for the taking of the most satisfactory phonocardiograms and the analysis and interpretation of these.

This atlas and short text is unreservedly recommended to any practitioner who wants to have a better knowledge of heart sounds and murmurs. It is a standard atlas of phonocardiograms of patients with various acquired and congenital lesions. Because of this book, phonocardiography is likely to assume a very prominent place in the diagnosis of those heart conditions which may be amenable to surgical treatment. Intracardiac phonocardiography taken with the microphone introduced into the cardiac chambers by catheterization was not mentioned, neither in the text nor in the figures that were shown.

Announcements

The Postgraduate School of Medicine of the University of Texas announces a course in PRACTICAL ELECTROCARDIOGRAPHY to be held in Houston, Tex., Dec. 15-19, 1958. This course will emphasize Spatial Vector-Electrocardiography. Dr. Robert F. Grant of the National Heart Institute, one of the foremost authorities in this field, will be the J.J. and Una Truitt Lecturer for this course. In addition to the evening formal lectures there will be daytime electrocardiographic interpretation practice sessions.

The Second Asian-Pacific Congress of Cardiology will be held in Melbourne, Australia, during the last week in May, 1960.

Further details may be obtained from Dr. A. E. Doyle, Honorary Secretary, Alfred Hospital, Melbourne S.1., Victoria, Australia.

The French Association of Cardiology has announced the formation of a French Association for the Study of Arteriosclerosis. This will be a section of the French Association of Cardiology.